DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

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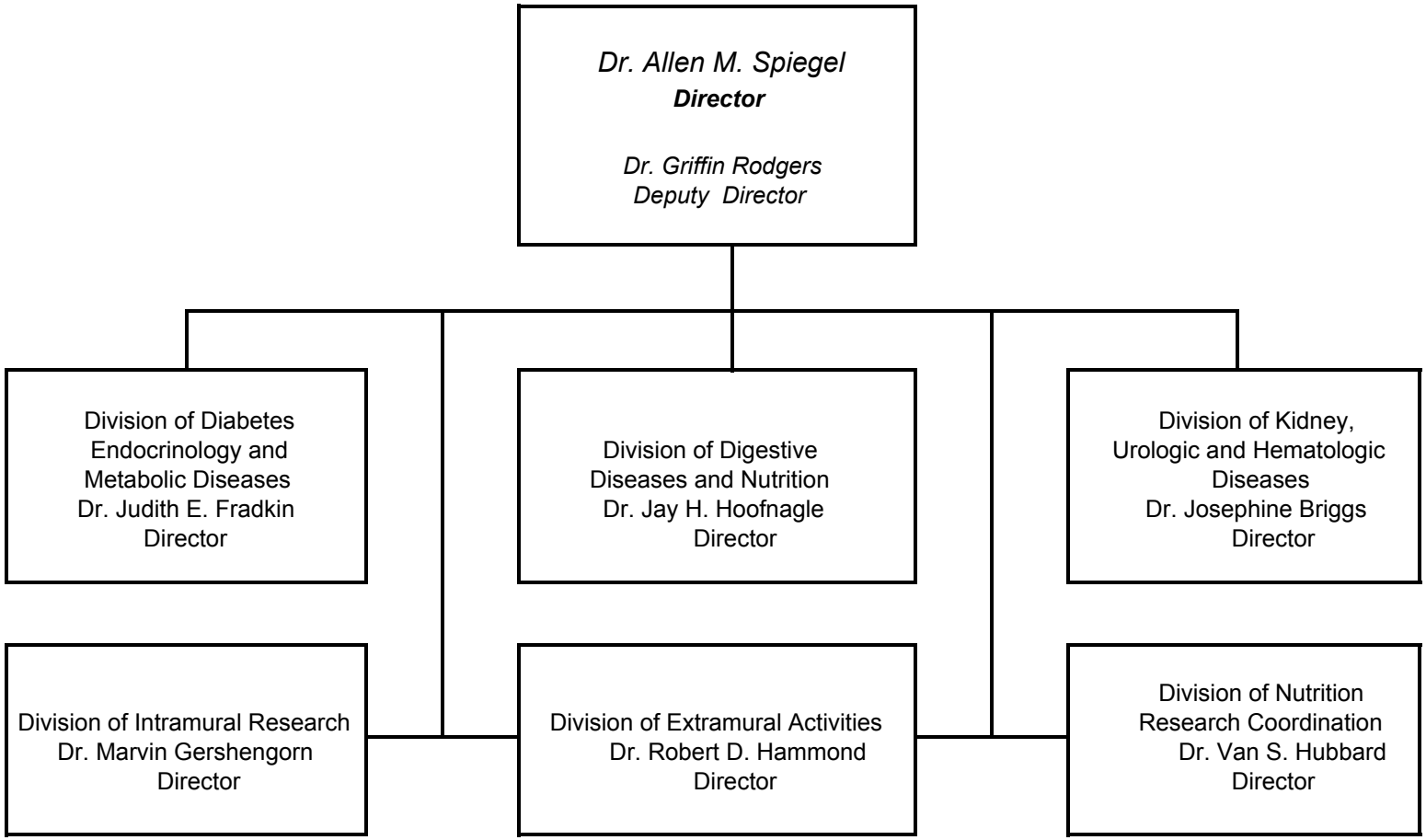
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases, $1,670,007,000.

National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

Source of Funding	FY 2002 Actual	FY 2003 Amended President's Budget	FY 2004 Estimate
Appropriation (Labor / HHS)	$1,466,833,000	$1,604,226,000	$1,670,007,000
Type 1 Diabetes 2/	$70,000,000	$100,000,000	$150,000,000
Enacted Rescissions	(1,689,000)	(0)	---
Subtotal, Adjusted Appropriation	1,535,144,000	1,704,226,000	1,820,007,000
Real transfer to:			
Other HHS Agencies through Secretary's one-percent transfer authority	(1,584,000)	(0)	(0)
Real transfer from:			
State Children's Health Insurance Program in the Health Care Financing Administration for Type 1 Diabetes Research	27,000,000	0	0
Comparative transfer to:			
Office of the Director for program changes	(1,097,000)	(1,185,000)	0
Fogarty International Center / VISA Program	120,000	120,000	
Subtotal, adjusted budget authority	1,559,583,000	1,703,161,000	1,820,007,000
Unobligated balance lapsing	(547,000)	---	---
Total obligations	1,559,036,000	1,703,161,000	1,820,007,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2002 - $10,067,000 FY 2003 - $10,250,000 FY 2004 - $10,500,000
Excludes $935,000 in FY 2002 and $960,000 in FY 2003 for royalties.

2/ Includes Type 1 Diabetes Funds in Accordance with P.L. 105-33, P.L. 106-554 and P.L. 107-360.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

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Authorizing Legislation: Section 301 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

	FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
	661		665		654		(11)	
Labor / HHS		$1,559,583,000		$1,703,161,000		$1,820,007,000		$116,846,000
Type 1 Diabetes		-$97,000,000		-$100,000,000		-$150,000,000		
Program Total		$1,462,583,000		$1,603,161,000		$1,670,007,000		$66,846,000

This document provides justification for the Fiscal Year 2004 research activities of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2004 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

The NIDDK conducts and supports research on many serious and costly chronic diseases affecting the public health. Several diseases studied by the NIDDK are among the leading causes of disability and death in the Nation; all seriously affect the quality of life of those suffering from them. The economic burden of these diseases represents a major proportion of U.S. health care expenditures. A focus on basic research has traditionally guided the Institute's programs. A fundamental understanding of biologic systems will ultimately explain the abnormalities underlying disease and thus is imperative for the development of the most effective strategies for prevention and therapy. In addition to basic research, the Institute has a strong commitment to transfer new knowledge of biologic processes into appropriate clinical studies, and ultimately, into efforts to translate knowledge and medical discoveries into improved health care, with special emphasis on populations disproportionately affected by diseases in the mission of the NIDDK.

The NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases is responsible for extramural research and research training related to diabetes mellitus; endocrinology, including osteoporosis; and metabolic diseases, including cystic fibrosis; this Division also supports research on obesity, a major risk factor for type 2 diabetes. The Division of Digestive Diseases and Nutrition has responsibility for managing research programs related to liver and biliary diseases;

gastrointestinal diseases, including motility, immunology, and digestive disorders; pancreatic diseases; nutrient metabolism; and obesity, eating disorders, and energy regulation. The Division of Kidney, Urologic, and Hematologic Diseases supports research on the normal and disease processes of the kidney, genitourinary tract, and the blood-forming organs to improve or develop preventive, diagnostic, and treatment methods. The Division of Intramural Research conducts research and research training within the Institute's laboratories and clinical facilities in Bethesda, Maryland, and Phoenix, Arizona. Shared interests in the biochemical and genetic processes underlying disease link the programs and divisions of the Institute, while close communication between the NIDDK and other NIH programs also fosters a confluence of fundamental knowledge in these vital areas of investigation.

Science Advances

Genetics and Genomics

Genomics and Diabetes Research: One of the key functions of the pancreas is to produce insulin; impaired insulin production causes type 1 diabetes and contributes to type 2 diabetes. To create the specialized cells of the pancreas, precursor cells during embryonic development begin to activate select genes that will equip their progeny cells with the necessary tools to become pancreatic cells. For example, scientists recently discovered in mice that a gene called *Ptf1a* is critical for directing cells to become pancreatic cells. Another gene, called *Pdx1,* was found to play a role both in pancreatic development and in maintaining the function of the mature pancreatic cells that secrete insulin to control blood sugar levels. To broaden knowledge of genes important for pancreatic development, a group of scientists capitalized on the large-scale genome analysis power of microarray technology. They imprinted a "chip" with a set of 3,400 pieces of DNA representing mouse genes that are active in the pancreas or otherwise known to be relevant to diabetes. They then used this unique microarray, or "PancChip," to track gene activity during pancreatic development, observing that the activity of different genes peaked at different times. The PancChip will now be provided to the diabetes research community as a cost-effective resource through NIDDK-supported biotechnology centers. Ultimately, a deeper understanding of pancreatic development and function may permit scientists to generate insulin-producing cells in the laboratory for use in treating diabetes.

Hereditary Hemochromatosis--A Common Mutation May Not Lead to Common Disease: Hereditary hemochromatosis is a genetic disease in which an abnormality in iron transport leads to iron accumulation in the body. Toxic iron levels can lead to a variety of health problems such as diabetes, heart arrhythmias, and cirrhosis of the liver. Several years ago, scientists discovered that hereditary hemochromatosis is caused by particular mutations in a novel gene that they termed *HFE*. With the ability to screen people for mutations in the *HFE* gene, it was theoretically possible to intervene early in the course of the disease and prevent target organ toxicity by iron overload. However, in a recent large study, researchers have now learned that most people who have these particular *HFE* mutations do not develop clinical symptoms and signs of organ toxicity. It is likely, then, that additional mutations or environmental factors influence whether a person who carries *HFE* mutations actually develops organ damage. This study suggests that widespread population screening for these *HFE* mutations would not be cost-effective. These findings will encourage scientists to search for other factors that contribute to hereditary hemochromatosis.

Developmental Biology

From Stem Cell to Specialized Cells--A Set of Genes Responsible for "Stemness," and Adult Progenitor Cells that Give Rise to a Remarkable Diversity of Specialized Cells: With the hope of one day replacing diseased or damaged tissue with normal cells, scientists are exploring stem and progenitor cells as possible sources of cells for therapeutic use. While embryonic stem cells may have the potential to develop, or "differentiate" into all of the body's specialized cell types, the extent of adult stem and progenitor cell potential has yet to be fully determined. It is also unclear how stem cells accomplish their dual tasks of self-renewal (to generate more stem cells) and differentiation into specialized cells--in other words, the two traits that define their "stemness." In one recent study, scientists analyzed genes that are turned on (expressed) in mouse embryonic stem cells and adult neural and blood stem cells but not in differentiated cells. Of all of the genes expressed in the stem cells, a core set of 216 genes was shared in common among all three stem cell varieties; this set of genes likely gives stem cells their "stemness." In another study, scientists identified adult bone marrow progenitor cells, from humans and rodents, that appear to have differentiation potential rivaling that of embryonic stem cells. The scientists coaxed these cells, called multipotent adult progenitor cells (MAPCs), to differentiate in the laboratory into an extraordinarily broad repertoire of specialized cell types, including blood vessel cell types, cells of the nervous system, and liver cells. They also demonstrated that the different specialized cell types did in fact arise from a single MAPC and were not simply descendants of several different progenitor cells. When put into mice, mouse MAPCs developed characteristics of specialized cells from a variety of tissues and organs but did not form tumors in the animals, an occurrence that has been associated with some embryonic stem cells. These studies open new opportunities for research on stem and progenitor cells and cell-based therapies.

Harnessing Technology

Developing Strategies To Overcome Immune Rejection of Transplants: The immune system will attack foreign material that enters the body--whether the material is infectious bacteria or viruses, or potentially life-saving cells and organs. Immunosuppressive agents help transplanted cells and organs survive in patients and play an additional role in "autoimmune" diseases such as type 1 diabetes. Since type 1 diabetes results from destruction of islet cells by an aberrant immune system, immunosuppressive agents may both reduce islet transplant rejection and help avert a recurrence of the immune attack that caused the disease in the first place. Researchers continue to seek improved immunosuppressive strategies. Recently, scientists developed a macaque monkey model of islet transplantation, a potential therapy for type 1 diabetes, based on an immunosuppressive strategy developed in Edmonton, Canada, for humans. Already, this primate model has enabled scientists to confirm that the site currently used for infusing islets into a patient, the portal vein of the liver, is superior to another site. In other studies in monkeys, scientists demonstrated that a new type of immunosuppressive agent not only reduces rejection of kidney transplants but it also enhances the survival of skin transplants. Exploration of immunosuppressive agents in animals will continue--with the goal of attaining the greatest therapeutic benefit with the least drug toxicity. These studies will likely benefit human health both through advances in immune modulation and through the development of animal models useful for optimizing other aspects of transplant procedures.

Gene Therapy in Dogs with Mucopolysaccharidosis VII (MPS VII): MPS VII is an inherited disease characterized by heart and eye abnormalities, poor growth, mental retardation, mobility problems, liver and spleen enlargement, and other serious symptoms. It is caused by a deficiency in the enzyme beta-glucuronidase. While treatments exist, they are not ideal. Researchers have now successfully used a new strategy to treat dogs with MPS VII--gene therapy. Based on earlier studies in mice, the scientists used a special genetically-engineered virus to insert a functional copy of the gene for beta-glucuronidase into liver cells of dogs with MPS VII. Their hope was that the liver cells would manufacture the enzyme and release it into the bloodstream to be carried to other affected organs. The treatment worked, preventing heart, eye and other symptoms that the scientists could assess in dogs. The scientists will continue to monitor the animals for potential adverse effects of the gene therapy. This research may one day lead to gene therapy treatments not only for MPS VII, but also for other diseases caused by deficiencies in blood or liver proteins.

Minority Health Disparities

Diabetes, obesity, hepatitis C, end-stage renal disease, benign prostate disease and several other diseases within the NIDDK research mission place a disproportionately heavy burden on racial and ethnic minority groups.

Progress Towards Eliminating Diabetes Health Disparities: Many minority groups have an increased risk of developing type 2 diabetes and also tend to suffer more from complications of the disease. Scientists are striving to better understand risk factors for this disease in minority populations and to develop better methods to manage it. In one study, researchers found that culturally-appropriate instruction in nutrition and other diabetes self-management topics is effective in improving the health of Mexican Americans with type 2 diabetes. Another group of scientists found that high insulin levels, which precede the development of type 2 diabetes, are associated with a skin condition called acanthosis nigricans in Cherokee Indians. These findings confirm and extend previous reports associating this skin condition with type 2 diabetes. Screening for this readily visible skin condition would provide a simple, inexpensive and non-invasive way to predict risk for type 2 diabetes, providing an opportunity for early intervention. In a third study, scientists found that Filipina American women are at much higher risk for type 2 diabetes than Caucasian women. However, Filipinas differ from Caucasians in that body mass index, typically used to assess overweight and obesity, did not correlate well with diabetes. For Filipina women, waist circumference and cholesterol measures were more useful for predicting diabetes. This study illuminates the importance of assessing risk factors for diabetes in diverse populations.

Diabetes

Strict Blood Sugar Control Helps Prevent Complications of Type 1 Diabetes over the Long Term: The landmark Diabetes Control and Complications Trial (DCCT) demonstrated that people with type 1 diabetes can dramatically reduce their risk for diabetes complications, including eye, nerve, and kidney disease, with an intensive treatment regimen to control their blood glucose (sugar) levels. An ongoing follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, has now shown that the benefits of this period of intensive blood glucose control persist for years. During the DCCT, patients were assigned to either intensive or conventional treatment groups. All trial participants were encouraged to use intensive treatment at the end of the trial. However, those who had been in the intensive treatment group during the trial still had a

significantly reduced risk of diabetes complications seven years later, even though by this time blood glucose levels had become similar in the two groups. Thus, it is important to begin intensive treatment to control blood sugar as early as is safely possible. Intensive control of blood glucose levels may also help patients with type 2 diabetes.

A Potential New Treatment To Preserve Insulin Production in Recent-Onset Type 1 Diabetes: In type 1 diabetes, the immune system attacks the insulin-producing beta cells of the pancreas. Eventually, type 1 diabetes patients must rely on daily insulin administration to stay alive. However, early in the course of the disease, the beta cells still produce some insulin, leaving a window for intervention to arrest the beta cell destruction. In a recent small-scale clinical trial, researchers gave patients with newly-diagnosed diabetes a new agent to modify the immune system to dampen its attacks on beta cells. Encouragingly, most of the patients maintained or improved the ability to produce their own insulin during the first year after being diagnosed with type 1 diabetes. This agent, an anti-CD3 monoclonal antibody, will now be tested in a larger number of patients.

People At High Risk For Type 1 Diabetes Can Be Identified, but Insulin Injections Do Not Prevent Disease: Because type 1 diabetes results from a decline in the body's ability to produce insulin, researchers once thought that giving insulin to people at high risk for diabetes might stave off this disease. In fact, based on animal data and small pilot studies in humans, some doctors began treating high-risk patients with insulin. A rigorous clinical trial has now shown that low-dose insulin injections do not prevent type 1 diabetes in people at high risk for this disease. While this was not the hoped-for result, it may potentially spare many patients from burdensome and ineffective therapy. Impressively, this trial showed that the scientists could accurately identify individuals at high risk for this disease, using a set of genetic, immunologic, and other biological tests. The ability to identify individuals at high risk for type 1 diabetes will facilitate future testing of promising new preventive agents--and ultimately help clinicians administer agents that prove effective to the patients who need them most.

Preventing or Delaying Type 2 Diabetes: Millions of Americans already suffer from type 2 diabetes, and this number will likely rise as the population ages and becomes increasingly overweight. Preventing diabetes is thus a critical research goal. In the highly successful Diabetes Prevention Program (DPP) clinical trial, scientists tested whether type 2 diabetes could be prevented in a study group of over 3,200 adults who were at risk based on excess body weight and blood sugar levels that were high but not yet in the "diabetic" range. The scientists found that a lifestyle modification that included modest weight loss and physical activity reduced the incidence of diabetes by 58 percent and was significantly more effective than the drug metformin, which reduced the incidence by 31 percent, as compared to a placebo. The lifestyle intervention was effective in men and women, in all of the many racial/ethnic groups studied, and in both older and younger adults. Another prevention trial focused on drug intervention in a particular group at high risk for type 2 diabetes, Hispanic women with previous gestational diabetes (diabetes during pregnancy). The incidence of type 2 diabetes in this group was reduced by at least 50 percent. The drug used is one of a class of agents that improve the body's sensitivity to insulin, a hormone essential for regulating blood sugar levels, and thereby may preserve the body's ability to produce insulin. Although the specific drug used in this study is no longer on the market, other drugs in this class are approved for diabetes and are being evaluated for preventing diabetes. By demonstrating that it is possible to delay or prevent the onset of type 2 diabetes and to reduce risk factors such as body weight, these trials provide ways to stem the rising tide of this devastating disease.

Elevated Cardiovascular Disease Risk Preceding Development of Type 2 Diabetes: In individuals with type 2 diabetes, the leading cause of death is cardiovascular disease. Even before diagnosis with type 2 diabetes, many patients already have risk factors for cardiovascular disease, such as elevated cholesterol and blood pressure. To further investigate these risks, researchers surveyed the health status of over 117,000 women during a 20-year period. The women who would later develop type 2 diabetes had a significantly increased risk of heart attack and stroke in comparison to non-diabetic women. The risks for cardiovascular disease began to rise at least 15 years before a diagnosis of type 2 diabetes. Thus, people at risk for type 2 diabetes or who have been diagnosed with "pre-diabetes" should be aware of and aggressively manage their underlying cardiovascular disease risk factors. This is an important health message that is being disseminated through the "Be Smart About Your Heart" campaign of the National Diabetes Education Program.

Stress Hormone May Direct the Body to Deposit Fat in the Abdomen, a Condition Associated with Diabetes: Excess weight is most ominous at the waist. Visceral fat in the abdomen, rather than total body fat, is the best predictor of obesity-associated diseases such as diabetes. Researchers have now determined that the stress hormone cortisol plays a key role in determining where fat is deposited in the body. In humans, high cortisol production has been found in visceral fat cells. To further understand visceral fat accumulation, scientists genetically-engineered mice to have fat cells containing extra amounts of a cortisol-producing enzyme. These mice ate more than normal, carried much of their increased weight around their middles, and developed insulin resistance and other metabolic conditions that are harbingers of type 2 diabetes. A drug already in use to treat type 2 diabetes reduces the activity of this cortisol-producing enzyme. The development of new strategies to target this enzyme may lead to new therapies for obesity and diabetes.

Endocrine and Metabolic Diseases

Developing New Technologies To Treat Cystic Fibrosis: Cystic fibrosis is caused by mutations in the gene encoding the CFTR protein. The most common mutation, called ΔF508, results in a misshapen CFTR protein that is unable to move to its proper location in the cell membrane. Left deep within the cell instead, it is nonfunctional. A group of researchers recently devised a novel strategy in mice to permit misshapen ΔF508-CFTR proteins to escape to the cell membrane and function properly; this method uses agents called calcium-pump inhibitors. Another strategy to treat cystic fibrosis would be to correct the mutation in the gene that encodes the CFTR protein, but this type of strategy has been fraught with extraordinary challenges. Scientists are now developing a creative alternative approach to correcting genetic mutations. Instead of correcting the mutation in the gene itself, the scientists seek to correct the mutation in the RNA copies of the gene that are used to synthesize the protein. A team of scientists was able to correct the ΔF508 mutation in the RNA copies of the *CFTR* gene in human cells grown in the laboratory, so that the cells could then make normal CFTR protein. Continued research into a diversity of treatment strategies will likely lead to new therapies for cystic fibrosis.

Story of Discovery: Leptin--A Potential Treatment for Lipodystrophy

In 1994, scientists discovered the mouse obesity gene and its protein product, leptin. The discovery that this protein is secreted by fat cells and is released in proportion to the amount of fat drastically altered the former view of normal fat tissue as a passive "fat storehouse." Research fueled by this discovery has also led to the identification of a number of other substances that, like leptin, are secreted by fat cells and influence appetite and metabolism. Leptin is secreted into

the bloodstream where it travels to the brain and signals the body to reduce food intake. Leptin may also affect one's food preferences and lessen one's craving for sweets. Leptin additionally affects the liver, muscle, and pancreas--organs that influence the body's ability to use fats and sugar. It can suppress the activity of an enzyme necessary for fat production and improve the sensitivity of muscle and other tissues to insulin, a hormone that regulates the body's storage and utilization of glucose, a key energy source.

Animals genetically deficient in leptin were found to be extremely obese. Because they lost weight when given leptin, researchers postulated that leptin treatment might also be useful for human obesity. There are, in fact, very rare instances of complete deficiency of leptin in humans, resulting in morbid obesity from infancy. Leptin treatment in these individuals caused substantial weight loss, providing hope for improved quality of life and longevity.

Unfortunately, in clinical studies leptin has not proven to be the panacea for the treatment of obesity in the vast majority of cases. With rare exceptions, obesity generally results from a complex interaction between our genes and our environment and lifestyle--particularly eating too much and exercising too little. Obese individuals, in fact, usually have very high levels of leptin, probably reflecting the many fat cells secreting it. The failure of all this leptin to decrease body weight suggests that the more common forms of obesity are associated with a resistance to leptin's actions.

Although leptin has not been a successful treatment for most cases of obesity, it has shown therapeutic promise for other disorders. A particularly fascinating example is lipodystrophy. This is actually a group of disorders with disparate origins but with a common set of characteristics. Individuals with lipodystrophy lack fatty tissue in the face, neck or extremities; they sometimes have central obesity and sometimes lack fat tissue altogether. These patients exhibit resistance to the effects of insulin and are at high risk of developing diabetes. They may also have a range of lipid abnormalities. Treatment of lipodystrophy has included insulin, oral hypoglycemic (blood sugar lowering) agents, and lipid-lowering drugs. In spite of treatment, patients continue to have severely high levels of triglycerides, leading to recurrent attacks of acute inflammation of the pancreas; severe problems controlling blood sugar levels, posing risks of diabetic eye and kidney disease; and fat accumulation in the liver, which can result in cirrhosis and liver failure. Because many lipodystrophy patients have low leptin levels, and because recent studies have demonstrated beneficial effects of leptin on insulin sensitivity and fat metabolism in a number of tissues, researchers investigated whether leptin treatments could ameliorate conditions associated with lipodystrophy.

Two recent publications reported exciting preliminary results of leptin treatment in small clinical studies of individuals with lipodystrophy. In one study, scientists found that leptin therapy markedly improved insulin sensitivity, lowered lipid levels, and decreased fat in the liver in individuals with severe lipodystrophy who also suffered from poorly controlled type 2 diabetes. After leptin treatment, the patients were also able to discontinue their diabetes medications. In addition, the patients had decreased appetite. In concomitant studies of lipodystrophy in animals, researchers found that leptin deficiency could explain most if not all of the confusing metabolic disturbances seen in this disorder.

In another study, researchers tested the effect of leptin in female patients with different forms of lipodystrophy, most of whom also had type 2 diabetes. During the study, most of the patients experienced significant improvements in their blood glucose levels, which in turn lowered their risk of developing diabetic eye and kidney complications. The leptin therapy also reduced their triglyceride levels. Liver size also decreased, indicating a loss of stored fat. Patients were able to reduce or stop using drugs to control their diabetes, and they reported eating less following treatment. Because of the dramatic improvement in their quality of life, the individuals in this study are continuing to receive leptin therapy.

Lipodystrophy can either be inherited or acquired. Researchers recently identified the genes responsible for two forms of inherited lipodystrophy; these findings may provide new therapeutic targets for lipodystrophy and other metabolic disorders. Lipodystrophy is often acquired by people infected with the human immunodeficiency virus (HIV) who are undergoing treatment with highly active anti-retroviral therapy (HAART). Although HAART has dramatically improved the survival of people with HIV, it is associated with a variety of metabolic complications, including elevated fat levels in the blood, insulin resistance, osteoporosis (bone loss) and lipodystrophy. The earlier success with leptin in treating lipodystrophy provides hope that it may be effective in HIV-associated lipodystrophy as well.

While lipodystrophy is characterized by loss of fatty tissue in certain areas of the body, tissues such as liver and muscle

exhibit significant abnormal accumulation of fat which impairs metabolic activity. Another condition marked by inappropriate accumulation of fat in the liver is non-alcoholic steatohepatitis (NASH), a disease most common in overweight adults over the age of 40. Individuals with NASH have insulin resistance, elevated levels of fats in their blood and a high risk of developing diabetes. Like obesity (but unlike lipodystrophy), NASH is correlated with high leptin levels. Thus, leptin resistance may play a role in the development of this disease.

The discovery of leptin has led to a cascade of exciting and unexpected findings with broad implications for the successful treatment of disease. While the initial excitement was tempered by the lack of success in countering obesity, leptin is now proving efficacious for treating less common disorders such as severe lipodystrophy. The promise that accompanied the discovery of leptin may yet be fulfilled, as future studies that do lead to effective tools to combat obesity will likely trace their origins to this remarkable discovery.

Obesity and Nutrition

Considering an Extra Helping? Gut Hormones that Influence Appetite and Weight: The appetite control center in the brain processes an array of signals that stream in from various parts of the body, including the gut. One of these signals, the hormone ghrelin, increases appetite and is produced by the stomach and small intestine. Scientists found that ghrelin not only stimulates appetite just before meals, but it also regulates body weight over the long term in ways that thwart dieters' best intentions for keeping off extra pounds. The scientists had a group of obese individuals follow a six-month dietary program, leading to a healthy weight loss. However, this weight change boosted the dieters' levels of ghrelin--a signal to eat more. By contrast, obese individuals who underwent gastric bypass surgery, a treatment for severe obesity, not only lost weight, but their ghrelin levels decreased. The effect of this surgical procedure on ghrelin levels may in part explain its success. In related work, scientists found that patients with Prader-Willi syndrome, a genetic syndromic obesity disorder, have elevated ghrelin levels. Ghrelin may thus contribute to their weight gain. If ghrelin is an internal adversary in the battle of the bulge, another gut hormone, PYY_{3-36}, is an ally. In a recent study, people given infusions of PYY_{3-36} had reduced appetite and decreased their calorie intake--even when presented with a free-choice buffet meal. Understanding the nature of hormones such as ghrelin and PYY_{3-36} may lead to new therapies to control appetite and achieve sustained weight loss.

Novel Approaches To Treating Obesity: New opportunities to develop treatments for the serious problems of overweight and obesity are emerging from increased understanding of normal weight regulation, and from innovative experiments with compounds that promote weight loss. One new study was based on knowledge that the hormone insulin reduces food intake and body weight when injected into the brain (of animals), but it does not have this effect when given systemically. Scientists tested the effects of small molecules that mimic insulin and found that these insulin "mimetics" decreased obesity--not only when injected into the brain--but also when given orally to rodents. Insulin mimetics might thus be useful therapeutically. Another research team investigated how the drug dexfenfluramine reduces food intake in animals. They discovered that it works through molecular pathways in the central nervous system. These findings may help in the design of improved weight loss drugs that act along these pathways, but that do not cause the side effects that led to the removal of dexfenfluramine from the market. In other studies in animals, scientists demonstrated the importance of proteins called beta-adrenergic receptors in regulating appetite and energy expenditure to prevent obesity. These diverse areas of research may lead to novel therapies for obesity, a health problem that has reached epidemic proportions.

A Genetic Locus for Severe Obesity: While sedentary lifestyles and unhealthy diets are contributing to the nation's rising epidemic of obesity, heredity also plays a role. However, the search for predisposing genes has been hampered by the genetic complexity of obesity. Now, in a collaboration between academia and industry, a team of investigators has found a chromosomal region (locus) linked to severe obesity in females. To design a genetic hunt to circumvent some of the genetic complexity of obesity, the scientists focused on very severely obese individuals. The more extreme a disease, the stronger the genetic influence is likely to be, and the greater the likelihood that it can be pinpointed. They also studied families with very obese members who were closely-related, and thus likely to share the same predisposing genetic variation. Additionally, the scientists incorporated strategies to detect potential gender-specific effects. With DNA samples from hundreds of people and sophisticated computer programs, the scientists pinpointed a locus on chromosome 4 that harbors a gene strongly linked to obesity in females. It is not yet clear whether it affects males. Future research will aim to identify the predisposing gene within this locus. Understanding how the gene functions could lead to drug development to modulate its effects on obesity.

Digestive Diseases

New Insights from Basic and Clinical Research on Hepatitis C: Hepatitis C virus is a common cause of liver disease in the U.S. Despite the proficiency of this virus in infecting humans, it tends not to infect small laboratory animals that would be useful research models. Scientists have now generated novel transgenic mice that make hepatitis C proteins, as if they had been infected with the virus. As a result, these mice accumulate excess fat in their livers and develop liver tumors--conditions commonly seen in human hepatitis C infections. From other aspects of the study, the scientists learned that the disease symptoms were caused by the viral proteins, although in human infection, disease may also result from the inflammatory response to the virus. Because current drug treatments eliminate the hepatitis C virus in some but not all patients, another research team recently investigated whether a vaccine would be a useful alternative means for protecting against disease. Vaccines for viral diseases are mock "infections" with a weakened virus or virus fragment that train the body to fight off later infections caused by a normal virus. To determine whether an exposure to hepatitis C virus can protect against later infection, scientists observed a group of people likely to have multiple exposures to this virus: users of injectable drugs. In many of these people, prior infection seemed to protect against subsequent, persistent infections, suggesting that a vaccine might help prevent serious liver diseases associated with viral persistence. The study also revealed that users of injectable drugs have an alarmingly high incidence of hepatitis C infection. These studies provide insights into how hepatitis C virus damages the liver and may spur new efforts toward vaccine development.

Genetic Loci Linked To Inflammatory Bowel Disease (IBD) in Mice: The inflammatory bowel diseases--Crohn's disease and ulcerative colitis--affect about one million Americans[1]. To search for genes that influence the severity of these genetically complex diseases, researchers used a technique called quantitative trait locus mapping to identify chromosomal regions (loci) that harbor such genes. The researchers first generated a set of mice that develop an IBD-like inflammatory disease but that have varying susceptibilities to gut inflammation. By quantitating the severity of disease

[1]Crohn's & Colitis Foundation of America, Library: Basic Facts: How Many Americans Have IBD? http://www.ccfa.org/medcentral/library/basic/news122.htm, posted January 1999; Loftus and Sandorn, Gastroenterol. Clin. North Am. 31: 1-20, 2002.

in the mice and correlating this with DNA sequence variations, the researchers identified loci linked to IBD severity, the most significant of which is on chromosome 3. Once scientists identify the genes within these loci that influence IBD in mice, they can use these as tools to find similar genes in humans that may also modulate this disease.

Potential New Therapeutic Strategy for Acute Pancreatitis: Acute pancreatitis is characterized by inflammation and destruction of pancreatic tissue. The disease is thought to begin when enzymes designed for food digestion mistakenly start digesting the pancreas. Cells of the pancreas produce these digestive enzymes in an inactive form for export to the intestines, where they then become activated and digest food. Premature activation of digestive enzymes in the pancreas can trigger the onset of pancreatitis. In recent experiments with rodent models of acute pancreatitis, scientists found that premature digestive enzyme activation can be reduced by giving the animals agents that inhibit a molecule called PI3K. The PI3K inhibitors also ameliorated the severity of disease in the animals. This study may lead to the development of PI3K inhibitors as novel therapeutic agents for acute pancreatitis in humans.

Story of Discovery: Genetic Insights into Pancreatitis and Pancreatic Cancer

When the pancreas produces enzymes to digest food, why don't those enzymes also digest the pancreas? Sometimes, they do--and with painful and potentially fatal consequences--as in the case of the disease hereditary pancreatitis. Several years ago, researchers discovered a mutation that abolishes one of the body's key safeguards against destruction of the pancreas by the very digestive enzymes it manufactures. This scientific breakthrough marked the beginning of a series of genetic discoveries that are providing new insights into hereditary pancreatitis, pancreatitis that arises for unknown reasons (idiopathic), and pancreatic cancer.

Patients with pancreatitis usually experience severe pain. As the pancreas becomes progressively injured and inflamed, in part as a result of infiltrating inflammatory cells, it no longer secretes enough enzymes into the small intestine for digesting food. Eventually, the pancreas cells that produce the vital hormone insulin can become damaged as well, leading to diabetes. Treatments exist to help manage the pain and digestive enzyme deficiency, but currently there are no cures or preventative therapies. Patients suffering long-term from pancreatitis are also at dramatically increased risk for pancreatic cancer. One of the most devastating of all malignancies, pancreatic cancer nearly always kills within a year of diagnosis, and often within six months.

Clinicians had long associated pancreatitis with alcoholism. While excessive alcohol consumption clearly plays a role in many pancreatitis cases, researchers recognized a hereditary form of pancreatitis as early as 1952. An attempt to find a hereditary pancreatitis gene in the 1970s, however, was unsuccessful. The identification of genes associated with pancreatitis awaited the advent of modern molecular and genetic technology.

In 1996, scientists found the first gene linked to a form of pancreatitis called hereditary pancreatitis, which generally strikes in childhood. This gene encodes the protein cationic trypsinogen, an inactive precursor form of the digestive enzyme trypsin. Trypsin helps digest proteins from food essentially by chopping them into pieces. To avoid digestion of the pancreas, trypsinogen normally does not become activated within the pancreas to form trypsin. If it does, the body has what scientists call a "fail-safe" line of defense: for the greater good, the prematurely-active trypsin commits molecular hara-kiri, slashing itself. Many people with hereditary pancreatitis have a particular mutation in the trypsinogen gene that disables this defense mechanism. Scientists have also identified other mutations in this gene. The continued identification of mutations that confer susceptibility to hereditary pancreatitis is useful for the design of diagnostic tests.

Among people whose genetic make-up predisposes them to hereditary pancreatitis, about one in five will not actually develop the disease. Surprisingly, researchers have even found pairs of identical twins in which one twin developed hereditary pancreatitis while the other did not, even though identical twins share the same chromosomal gene sequences

and most types of environmental factors. These findings clearly suggest that other types of genetic factors (such as "epigenetic factors"), environmental factors, or chance events may also play a part in the development of hereditary pancreatitis. Scientists believe that pancreatitis results from a long chain of events activating different enzymes. In addition to known genetic influences, the disease is also precipitated by external factors such as food and alcohol. Gaining a better understanding of the complex interactions between different types of genetic and environmental factors will be a major challenge for future investigations.

Knowledge of genetic influences in hereditary pancreatitis will also help scientists assess environmental risk factors for pancreatic cancer, because people with hereditary pancreatitis are at increased risk for this cancer. Scientists recently found that pancreatic cancer develops an alarming 20 years earlier in hereditary pancreatitis patients who smoke. It is not yet clear whether smoking also has this effect in people who don't have hereditary pancreatitis.

Several years after the discovery that mutations in the trypsinogen gene cause hereditary pancreatitis, scientists identified mutations in a different gene that are associated with idiopathic pancreatitis. This gene encodes a protein called SPINK1, which normally helps protect the pancreas by inhibiting the digestive functions of prematurely-activated trypsin. However, the effects of *SPINK1* mutations are subtle, and dissecting the nature of their association with pancreatitis remains challenging.

The identification of another gene associated with idiopathic pancreatitis had its origins in research on a seemingly unrelated disease, cystic fibrosis, which is caused by mutations in the *CFTR* gene. *CFTR* function is important in many organs, including the pancreas, and scientists recently found that many idiopathic pancreatitis patients harbor a particular pattern of *CFTR* mutations.

With the discovery in 1996 of the link between trypsinogen and hereditary pancreatitis and the findings in 1998 and 2000 that *CFTR* and *SPINK1* are associated with idiopathic pancreatitis, it would seem that another major genetic discovery in pancreatic disease might arrive in 2002. One did. Investigators have now brought to light the first genetic defect specific to pancreatic cancer, pinpointing a region on chromosome 4 as likely to contain a pancreatic cancer susceptibility gene. The future identification of this gene will enhance our understanding of pancreatic cancer and provide a potential tool for early diagnosis.

Screening patients for genetic mutations can have many health benefits, such as alerting patients at risk to seek early medical intervention. However, the results of a genetic test may also influence reproductive choices and the ability to obtain health or life insurance. Deeply concerned about the ethical and social implications of genetic testing for patients and their families, investigators recently surveyed individuals participating in a hereditary pancreatitis genetic research study. The most common reasons the participants gave for joining the study were to help family members and future generations and to obtain genetic testing. The major concern they expressed was the fear of insurance discrimination. The most common reasons for sharing their results were to provide medical information to their families and to improve their own medical care.

These achievements in research on pancreatitis and pancreatic cancer not only illuminate genetic influences underlying these diseases, but also will facilitate research on environmental factors that contribute to disease in genetically-susceptible individuals. Already, the identification of hereditary pancreatitis mutations has led to the development of gene-based methods to evaluate a person's risk for this disease. Further understanding of genetic factors associated with different forms of pancreatitis and pancreatic cancer will undoubtedly lead to new strategies for diagnosis, treatment, and prevention.

Kidney, Urologic, and Hematologic Diseases

Poor Growth Further Disadvantages Children on Dialysis: Children on dialysis for kidney failure are at greater risk of death if they also have poor growth. In a new study of over 2,300 children, researchers found that poor growth preceding the initiation of dialysis is also associated with increased health problems once dialysis treatments have begun. The researchers used height as a

marker for growth during the period of progressive kidney disease leading to the need for dialysis. The children with short stature at the initiation of dialysis, reflective of poor growth, had more hospital stays, were less likely to attend school full time, and were at two-fold greater risk of death compared to children with more normal growth. This study reaffirms that measures to improve growth, including nutritional support and other medical interventions, should be taken before kidney disease progresses to end-stage, in order to maximize the long-term health of children on dialysis.

Polycystic Kidney Disease (PKD) Genes in Animal Models: Mutations in a number of different genes can cause PKD, a serious kidney disease. To gain clues as to how disruptions in these genes derail normal kidney function, scientists are studying animal models. Recently, scientists identified a new gene which, when mutated, causes PKD in mice. The proteins encoded by this gene and another PKD-related gene both appear to function in the cilia of kidney cells. Cilia are hair-like projections that can be used as "antennae" to help cells sense and respond to changes in the local environment. In other studies, researchers found that the worm *C. elegans* has genes that are very similar to two of the human genes associated with PKD. Mutations in these genes cause biological problems for the worms, and, intriguingly, the proteins encoded by the genes are enriched in the cilia of certain cells. By hinting that PKD may result from improper functioning of the kidney cell cilium, these studies will help guide further PKD research.

Stretching of the Urinary Bladder Causes a Host of Cellular Changes: As the bladder fills with urine and increases in volume, the cells lining the bladder must ensure that no leakage to underlying muscle and other tissues occurs. To understand this process, scientists used a sophisticated machine to stretch bladder tissue from a rabbit, to simulate bladder expansion, and then observed the cells. Previously, it was thought that as the bladder fills, cells lining the inner surface of the bladder, called "umbrella" cells, increase their membrane surface area simply by unfolding existing membrane structure, like the unfolding of an umbrella. By contrast, the scientists found that the expanse of membrane at the cell surface actually increased through the addition of new membrane, obtained from small membrane-enclosed sacs, called vesicles, which are sent out from within the cell to fuse with the cell membrane. Surprisingly, the cells also pulled bits of membrane back into themselves. The balance between these two processes may help the cells fine-tune the size of their membranes. The umbrella cells also became longer and shallower in response to the stretch. This fundamental knowledge of bladder cells may lead to better treatments for bladder disorders.

Story of Discovery: Cardiovascular Disease and Kidney Disease: Teasing Out the Link

Are two diseases related or just coincident? Sometimes the answer comes through careful analyses of large sets of numbers--numbers of patients and their associated risk factors. In the case of kidney disease and cardiovascular disease, such epidemiologic studies have pointed to a connection between end-stage renal (kidney) disease and risk of cardiovascular disease. Now researchers are faced with teasing out answers to the question: why?

The United States Renal Data System (USRDS), established in 1987, is a national data system that collects, analyzes, and distributes information about end-stage renal disease in the United States, and is supported by the NIDDK in conjunction with the federal Centers for Medicare and Medicaid Services. End-stage renal disease (ESRD) is a state of irreversible kidney failure in which a person requires either dialysis or a kidney transplant in order to stay alive. The USRDS has collected comprehensive data on over 92 percent of Americans with ESRD and releases an Annual Data Report every year; researchers can then analyze these data to discover emerging trends in both causes of ESRD and causes of death in ESRD patients.

A connection between ESRD and death due to cardiovascular disease (CVD) in a small number of patients on hemodialysis was noted nearly three decades ago. However, it is the careful analysis of patient data available in the USRDS database that has enabled researchers to recognize the enormity of the connection between patients requiring dialysis and their subsequent deaths from CVD. According to the latest Annual Data Report (2002), CVD (primarily coronary artery disease, left ventricular hypertrophy, atherosclerotic heart disease, and congestive heart failure) is the leading cause of death in ESRD patients. Studies using recent USRDS data revealed that death rates from CVD in dialysis patients are 20 to 40 times higher than in the general population[2], and an extensive retrospective study showed that 73 percent of dialysis patients who suffer a heart attack die within two years.[3]

The figures for mortality due to CVD in ESRD are striking--and ominous. Groups at highest risk for developing ESRD include the estimated 17 million Americans with diabetes[4], the elderly, and ethnic minorities, as well as people with hypertension, genetic renal disease, or a family history of renal disease. The population at risk for developing CVD independent of ESRD is very similar to the population at risk for ESRD. In fact, some of the risk factors for CVD are indistinguishable from those for ESRD. Furthermore, researchers recently reported a higher prevalence of many traditional CVD risk factors in ESRD patients than in the general population.

Studying the USRDS numbers, epidemiologists realized that rates of pre-existing CVD in people initiating dialysis are very high, approximately 40 percent.[5] This led researchers to suspect that CVD is developing during pre-ESRD states. Before ESRD, there is a prolonged state of progressive loss of renal function, referred to as chronic kidney disease. The degree of chronic kidney disease is established by measuring how efficiently the kidneys can filter out toxins from the blood, known as the glomerular filtration rate. When glomerular filtration rate decreases, bloodstream levels of a number of waste products increase. Small studies recently indicated that, just as in ESRD, there are higher rates of death from CVD in people with chronic kidney disease. A recently launched prospective study, the "Chronic Renal Insufficiency Cohort," will assess risk factors for both the progressive decline in kidney function and the development of CVD in a large study population with chronic kidney disease. Through careful data analysis, the scientists aim to determine whether chronic kidney disease causes CVD or is simply associated with it.

Although defining the link between chronic kidney disease and risk factors for developing CVD awaits the outcome of large prospective studies, researchers can still test ideas as to how factors traditionally associated with decreasing kidney function--uremia-related factors--might in fact also lead to CVD. Basic research studies have contributed significantly to a number of hypotheses about how observed uremia-related factors might increase the risk of developing CVD, including the following:

Uric Acid: Uric acid is a waste product of nitrogen metabolism. It is normally present in the bloodstream, where it is thought to act beneficially as an antioxidant. However, impaired renal function can lead to uric acid levels that are too high, causing health problems such as gout. Elevated blood levels of uric acid may also be associated with a greater risk of heart disease, although the epidemiologic data are still under debate. A recent study in rats suggests a possible mechanism for uric acid's proposed role in CVD, showing that elevation of uric acid increases blood pressure and causes kidney injury. The human gene encoding the uric acid transporter responsible for uric acid recovery from the kidney tubules was recently identified by researchers in Japan; now, its activity in chronic kidney disease and ESRD can be tested.

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[2]Collins et al. Am. J. Kidney Dis. 38: S26-9, 2001; Sarnak and Levey. Seminars in Dialysis 12: 69-76, 1999.

[3]Herzog et al. N. Eng. J. Med. 339: 799-805, 1998.

[4]National Institute of Diabetes and Digestive and Kidney Diseases, National Diabetes Statistics, March 2002, http://www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm#7; Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Diabetes Public Health Resource: National Diabetes Fact Sheet, March 2002, http://www.cdc.gov/diabetes/pubs/estimates.htm.

[5]Sarnak and Levey, Am. J. Kidney Dis. 35: S117-31, 2000.

Salt-sensitive Hypertension: There is evidence in animal models that subtle renal injury, induced by local inflammation and vasoconstriction, may interfere with normal salt excretion from the kidneys. Sodium dysregulation in particular may, in turn, raise blood pressure and further damage the kidney, initiating a vicious cycle, resulting in permanent salt-sensitive hypertension that promotes CVD.

Homocysteine: Homocysteine is a modified form of the essential amino acid methionine. Normal blood levels of homocysteine are maintained primarily by the activities of folic acid, vitamin B12, and vitamin B6. Deficiency in these vitamins can lead to hyperhomocysteinemia (high levels of homocysteine)--as can decreased glomerular filtration rate. Mild to moderate hyperhomocysteinemia appears to contribute to CVD outcomes in both the general population and persons with ESRD. Although successful in the general population, B-vitamin supplementation is not efficacious in lowering homocysteine in ESRD patients; however, it does normalize homocysteine levels in both renal transplant patients and mild chronic kidney disease patients. A study called FAVORIT is now testing whether high-dose supplementation with folic acid, vitamin B12, and vitamin B6 will improve CVD outcomes in chronic kidney disease patients and stable renal transplant patients.

As scientists develop testable hypotheses about how chronic kidney disease might induce CVD, they will be able to shore up epidemiologic data with mechanistic data to explain any observed link between these two conditions, and move towards possible prevention and treatment of CVD induced by chronic kidney disease. Through these efforts, future analysis of data from the USRDS will hopefully become the more optimistic task of documenting a steady reduction in cardiovascular disease-related mortality in patients with end-stage renal disease.

Blood Stem Cells as a Potential Therapy for Sickle Cell Anemia: For patients with sickle cell anemia, a serious inherited blood cell disease prevalent in African Americans, the only curative treatment available is a bone marrow transplant. With recent advances in blood stem cell technology, transplants of blood stem cells could become an advantageous alternative to bone marrow transplants to replace the impaired, "sickle"-shaped red blood cells with healthy cells. A patient's sibling is likely to be an eligible blood stem cell donor due to certain genetic traits that may be shared in common among siblings. However, siblings of patients with sickle cell anemia have at least a 50 percent chance of having inherited a related disorder called sickle cell trait. While less severe than sickle cell anemia, sickle cell trait is associated with complications. Thus, it was not clear whether a method for obtaining large numbers of blood stem cells, involving the use of a stem-cell "mobilization" agent, would be safe in people with sickle cell trait. Scientists have now found that this method appears to be safe in individuals with this disorder, thus permitting them to donate blood stem cells for a potential new treatment of sickle cell anemia.

AIDS

Positive and Negative Metabolic Effects of Growth Hormone Therapy in HIV-Positive Individuals with Fat Accumulation: Prolonged, highly active antiretroviral therapy (HAART) for HIV infection is associated with a potentially serious metabolic syndrome that may result in the redistribution of body fat, lipid abnormalities, and insulin resistance or diabetes. Treatment of HIV-positive individuals who have central fat accumulation with human growth hormone (hGH) reduces total body and visceral fat and increases lean tissue mass, but also can decrease insulin sensitivity. A recent study examined the contribution of the liver to changes in insulin sensitivity and fat metabolism during hGH therapy. Treatment with hGH improved the overall lipid profile, resulting in a decrease in triglycerides and total cholesterol and an increase in HDL (good) cholesterol concentration. However, hGH treatment was also associated with insulin resistance in

the liver and other tissues. This study clarifies the potential risks and benefits of hGH therapy for the HIV- and HAART-related metabolic syndrome. This research has implications for the design of therapeutic strategies to mitigate the unwanted metabolic effects of HAART.

Initiatives

In FY 2004, the NIDDK will pursue multiple and diverse avenues of fundamental and clinical research relevant to the diseases within its mission.

Diabetes, Endocrinology, and Metabolic Diseases: The NIDDK is fostering multidisciplinary research through a variety of consortia focused on important fundamental and clinical research issues. Support will continue for a Beta Cell Biology Consortium to facilitate interdisciplinary approaches that will advance understanding of pancreatic islet development and function. The NIDDK will enhance fundamental research on fat cells and fat tissue. A new long-term effort is being launched to identify environmental factors associated with development of type 1 diabetes. To foster collaborations between clinical and basic scientists with the goal of translating fundamental research advances into new therapies, a bench-to-bedside research initiative on type 1 diabetes and its complications will be reissued. Training and career development programs in diabetes research for pediatric endocrinologists have recently been established. A new effort will pursue increased knowledge of androgen receptor signaling in the prostate to better understand prostate growth and cancer. Support will be provided for the use and development of proteomics technologies for studying diabetes and other endocrine and metabolic diseases.

The NIDDK will continue vigorous support of its clinical trials programs. In the area of type 1 diabetes, an ongoing trial is testing a regimen of steroid-free immunosuppression to prevent islet cell rejection following transplant. An ongoing arm of the *Diabetes Prevention Trial--Type 1 Diabetes (DPT-1)* is designed to determine whether oral insulin administration can delay or prevent the onset of type 1 diabetes in individuals at risk for the disease; this study is being carried out by TrialNet, a clinical research network. TrialNet will also begin studies aimed at preserving beta cell function in patients with new onset type 1 diabetes. Another study will seek to improve treatment of depression in children with type 1 diabetes. The *Diabetes Prevention Program (DPP)* clinical trial demonstrated that type 2 diabetes could be delayed or prevented with either lifestyle modification or metformin in adults at high risk, including minorities who suffer disproportionately from the disease. The NIDDK now plans long-term follow-up studies to address the durability of the DPP interventions in preventing or delaying diabetes and to determine whether the interventions reduce cardiovascular disease and atherosclerosis. The Institute will begin research on prevention and treatment strategies for type 2 diabetes in children. A pilot study is planned to test leptin as a treatment for children with severe insulin resistance syndrome. Another effort will strive to develop more effective ways to translate into improved health care practices the results of large clinical trials such as the DPP, for type 2 diabetes, and the Diabetes Control and Complications Trial, for type 1 diabetes.

Digestive Diseases and Nutrition: The NIDDK will intensify its efforts to combat obesity as a serious health problem and as a risk factor for type 2 diabetes. One facet of this research will be to promote clinical research on bariatric surgery, currently used in treating extreme obesity, to better understand the impact of bariatric surgical procedures on obesity and related co-morbid conditions. Research will be bolstered on hepatitis C virology, epidemiology, natural history, prevention, and

therapy--potentially including research on therapy in children. Recently, the Institute launched a new effort to elucidate the clinical features and pathogenesis of drug- and toxin-induced liver injury, a common cause of acute liver disease, morbidity, and mortality. New insights will be sought into intestinal failure, short gut syndrome, and small bowel transplantation. To strengthen research in inflammatory bowel disease (IBD), efforts will be accelerated to identify additional genes or genomic regions associated with increased risk of IBD or with clinical manifestations of IBD.

In the area of clinical trials in digestive diseases, including obesity, the *Look AHEAD (Action for Health in Diabetes)* multicenter clinical trial is under way and has reached approximately the midpoint of its recruitment goal of 5,000 individuals. This long-term clinical trial is designed to answer two major questions. First, do interventions designed to produce voluntary sustained weight loss in obese people with type 2 diabetes improve health, particularly with respect to cardiovascular outcomes? Second, how do these interventions compare with treating obesity-related conditions without weight loss? Results of this study will help guide future patient care. The NIDDK is continuing enrollment of patients in the multi-center *Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C)* clinical trial. This trial is designed to investigate whether long-term treatment of hepatitis C with peginterferon alfa will prevent progression of liver disease in patients for whom prior treatment did not eliminate the virus. Enrollment has also begun for the *Virahep-C* study, which will examine resistance to antiviral therapy in patients with chronic hepatitis C, specifically focusing on African Americans, among whom such viral resistance is common. New clinical research efforts are also now beginning on non-alcoholic steatohepatitis and biliary atresia, and on outcomes of adult-to-adult living donor liver transplantation.

Kidney, Urologic, and Hematologic Diseases: Basic research on the bladder will be strengthened based on recommendations from the NIDDK-sponsored Bladder Research Progress Review Group; additionally, to propel research towards better understanding of interstitial cystitis, increased support will be provided for basic cellular, molecular, and genetic studies pertinent to this disease. The Institute will promote the development of research tools and innovative methods for studying the individual cell types of the bladder, prostate, and genitourinary tract. Complementing a prospective cohort study of chronic renal (kidney) insufficiency in adults will be a new study of chronic renal insufficiency in pediatric patients. The therapeutic potential of hematopoietic (blood) stem cells will be advanced through hematopoietic cell lineage genome anatomy projects. To help guide therapy for anemias and other blood disorders, MRI technology will be explored as a potential non-invasive way to measure body or tissue iron.

In addition to supporting fundamental research in kidney, urologic, and hematologic diseases, the Institute will continue its strong support of clinical trials. Men with symptomatic benign prostatic hyperplasia (BPH) suffer from increased urinary urgency, frequency, and nighttime urination, leading many to eventually seek surgical treatment. The clinical trial on *Medical Therapy of Prostate Symptoms (MTOPS)* recently demonstrated that two drugs commonly used to treat BPH, finasteride and doxasozin, are significantly more effective at preventing symptomatic BPH incidence and progression when given in combination. Together, they reduced risk of progression of BPH by 67 percent, *versus* 39 percent with doxasozin alone and 34 percent with finasteride alone. The *Minimally Invasive Surgical Therapies (MIST) Treatment Consortium for BPH* is designing trials to assess the safety and efficacy of new surgical treatments for BPH; the first trial will include evaluation of the combination of surgery with a drug regimen similar to that used in *MTOPS*. Samples collected during the *MTOPS* trial will be used by the *MTOPS Prostate Samples Analysis*

Consortium to discover and validate biologic markers or genetic susceptibility tests for detection, risk assessment, and disease assessment of BPH. The *HEMO* clinical trial has shown that the standard recommended hemodialysis dosage and filters are adequate for reducing morbidity and mortality in end-stage kidney failure patients and that increasing dialysis dose using a conventional three times per week regimen does not provide greater benefit to patients. The *Dialysis Access Consortium* is launching two clinical trials to evaluate methods to improve blood vessel access in hemodialysis. To gain further insights into the relative benefits of different modes of dialysis to improve patient care, studies will evaluate intensive dialysis in patients with acute renal failure. Further, *Daily Dialysis* randomized clinical control trials will be developed to compare conventional dialysis with more frequent dialysis in patients with end-stage renal disease. Newly launched studies include the *Family Investigation of Nephropathy and Diabetes*, a multi-center consortium to study genetic susceptibility in diabetic kidney disease. The Institute is also initiating *Complementary and Alternative Therapy for Benign Prostatic Hyperplasia*, a large clinical trial to examine the effects and efficacy of two commonly used alternate therapies for BPH, saw palmetto and *Pygeum africanum*. The *Focal Segmental Glomerulosclerosis (FSGS) in Children and Young Adults* clinical trial is being initiated to examine interventions to prevent progression of FSGS, a disease which can lead to kidney transplant injury or loss. The NIDDK has also established a *Polycystic Kidney Disease (PKD) Clinical Trials Network* to design and implement clinical trials of agents that might slow progressive loss of kidney function in PKD.

Trans-NIDDK: The NIDDK is planning to establish central facilities for archival storage of biosamples and data collected in large, multi-site studies, and for processing of genetic samples. Central repositories will enhance the value of large studies by increasing access to the biosamples and data that have been collected and by facilitating efficient sharing of these resources. Following a recent workshop on hepatitis C and renal disease, the NIDDK is planning to intensify research in this area. The NIDDK will expand its Diabetes Genome Anatomy Project (DGAP) to identify the genes important in the pancreas and other tissues affected by diabetes. Multiple large-scale genome anatomy projects (GAPs) have been or are being created by the NIDDK to develop and apply genomic approaches to basic and disease-related research areas. To build on these projects, a program is planned to link the GAPs with individual investigator-initiated projects. A number of diseases are influenced primarily by a single gene, yet symptoms vary among individuals, likely as a result of "modifier" genes. The NIDDK will strive to identify such modifier genes to provide potential new targets for diagnostic or therapeutic strategies.

AIDS: Research efforts will advance understanding of co-infections that occur in patients with HIV infection. These efforts will include further investigation into the frequent co-incidence of hepatitis C and HIV infection. Additionally, the set of metabolic complications associated with treatment of HIV is an important area of focus with respect to research on fat cells and lipodystrophy. Finally, the Institute will continue to support research on the liver and pancreatic complications of both HIV infection and its therapy.

Strategic Planning: In framing new and expanded initiatives, the NIDDK continues to be guided by several strategic planning efforts. A recently completed report of a group of external experts, the Bladder Research Progress Review Group, provides an important assessment of the state-of-the-science in the field and useful recommendations for future research directions. Similarly, the Institute has provided a mandated report to the Congress which highlights program efforts, research advances and opportunities in diabetes research since the issuance of the 1999

Strategic Plan of the Congressionally-established Diabetes Research Working Group. During the coming year, the NIDDK will consult with external scientific experts to develop a Liver Disease Research Action Plan. These are just some examples of how the Institute works closely with experts in many scientific disciplines to help ensure that its program development efforts are exploiting cutting-edge scientific opportunities.

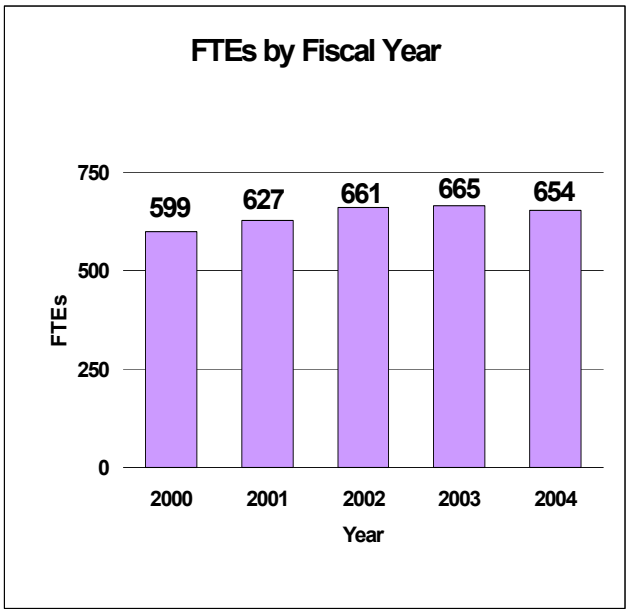
Educational Programs: Through a variety of educational programs, the NIDDK will continue to provide important health information to health practitioners and the public. The National Diabetes Education Program (NDEP) is a partnership among the NIDDK, the CDC, and over 200 public and private organizations. The NDEP's "Be Smart About Your Heart: Control the ABC's of Diabetes" campaign promotes control of hemoglobin A1c (reflecting blood glucose), blood pressure, and cholesterol. The NDEP is now developing a campaign to translate the impressive results of the Diabetes Prevention Program (DPP) to the general population, with culturally sensitive public health messages and intervention strategies. It will focus on the message that there is a pre-diabetes state when prevention of type 2 diabetes is possible, and that modest improvements in diet and physical activity yield major benefits. Recently, the NDEP launched a new campaign to help Hispanic Americans better understand the need to control their diabetes to help prevent heart disease. The NIDDK is supporting the development of diabetes-focused science education programs in Tribal middle and high schools with the dual goals of increasing diabetes awareness with a view toward prevention among American Indian youth, as well as increasing the number of American Indians in biomedical science careers. The NIDDK's Weight-control Information Network (WIN) produces and provides materials on obesity, weight control, physical activity, and nutrition. Recently, WIN began publishing a new series of booklets on "Healthy Eating and Physical Activity Across Your Lifespan" with versions in both English and Spanish. WIN is continuing its "Sisters Together: Move More, Eat Better" theme that encourages African American women to maintain a healthy weight. WIN is also coordinating with the Institute's Look AHEAD clinical trial to provide information on physical activity and healthy eating to trial participants. This trial will examine whether a lifestyle intervention designed to achieve voluntary long-term weight loss will improve cardiovascular and other outcomes in obese individuals with type 2 diabetes. The NIDDK recently launched the National Kidney Disease Education Program (NKDEP), a pilot program that aims to prevent kidney disease by raising awareness about the seriousness of the problem and the importance of early diagnosis, and appropriate treatment. Despite evidence that kidney failure may be prevented or slowed through control of blood pressure with ACE inhibitors and control of blood glucose, about 269,000 Americans require dialysis and nearly 100,000 more are sustained by kidney transplants to stay alive.[6] NKDEP is designed to close the gap between evidence and practice. NKDEP will initially target primary care providers and people at highest risk for kidney disease--particularly African Americans with diabetes, high blood pressure or a family history of kidney disease--in four cities on a pilot basis: Baltimore; Cleveland; Jackson, Mississippi; and Atlanta.

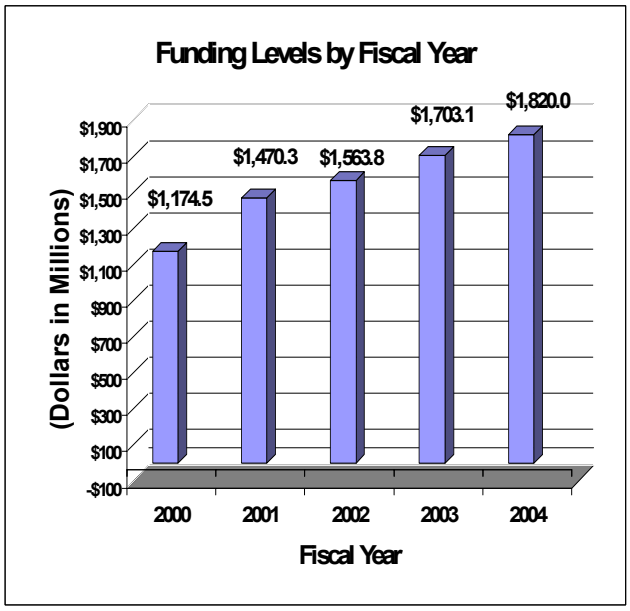
Budget Policy

The Fiscal Year 2004 budget request for the NIDDK is $1,820,007,000 including AIDS, an increase of $116,846,000 and 6.8 percent over the FY 2003 amended President's Budget Request. A five

[6]United States Renal Data System. USRDS 2002 Annual Data Report, National Institutes of Health, National Institute of Diabetes, Digestive, and Kidney Diseases, Bethesda, MD; 2002, pp. 44-45.

year history of FTEs and Funding Levels for NIDDK are shown in the graphs below. Note that Fiscal Years 2001 and 2000 FTEs are not comparable for the NIH Human Resources functional consolidation.





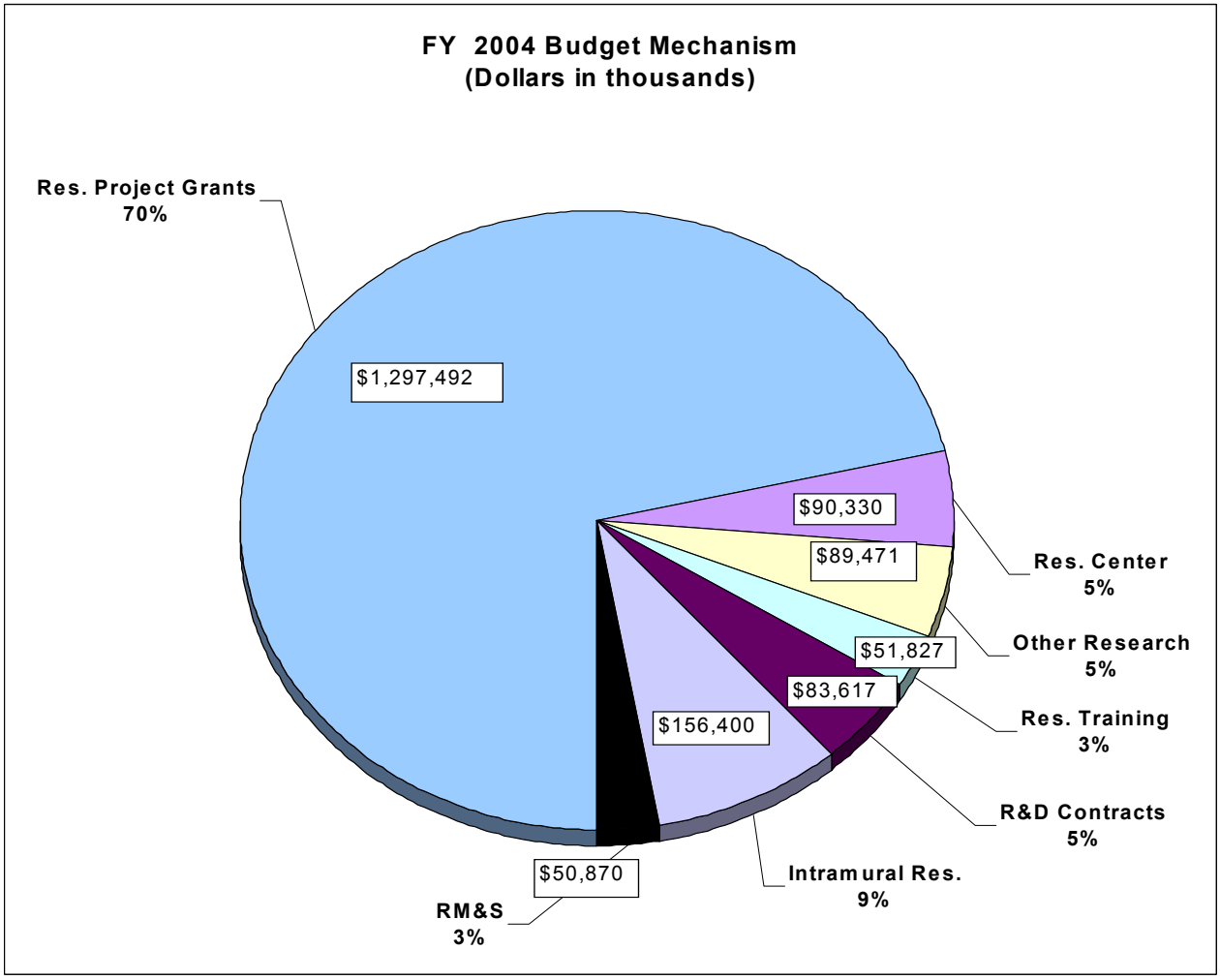
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. NIDDK will provide an aggregate average cost increase of 1.9 percent for Research Project Grants (RPGs). This is the overall impact of the FY 2004 NIDDK direct appropriation request of $1,670,007,000 before the effect of the FY 2004 Type One Diabetes funds are included in the program total. The Type One Diabetes funds appropriation is increasing by $50,000,000 over the FY 2003 level of $100,000,000.

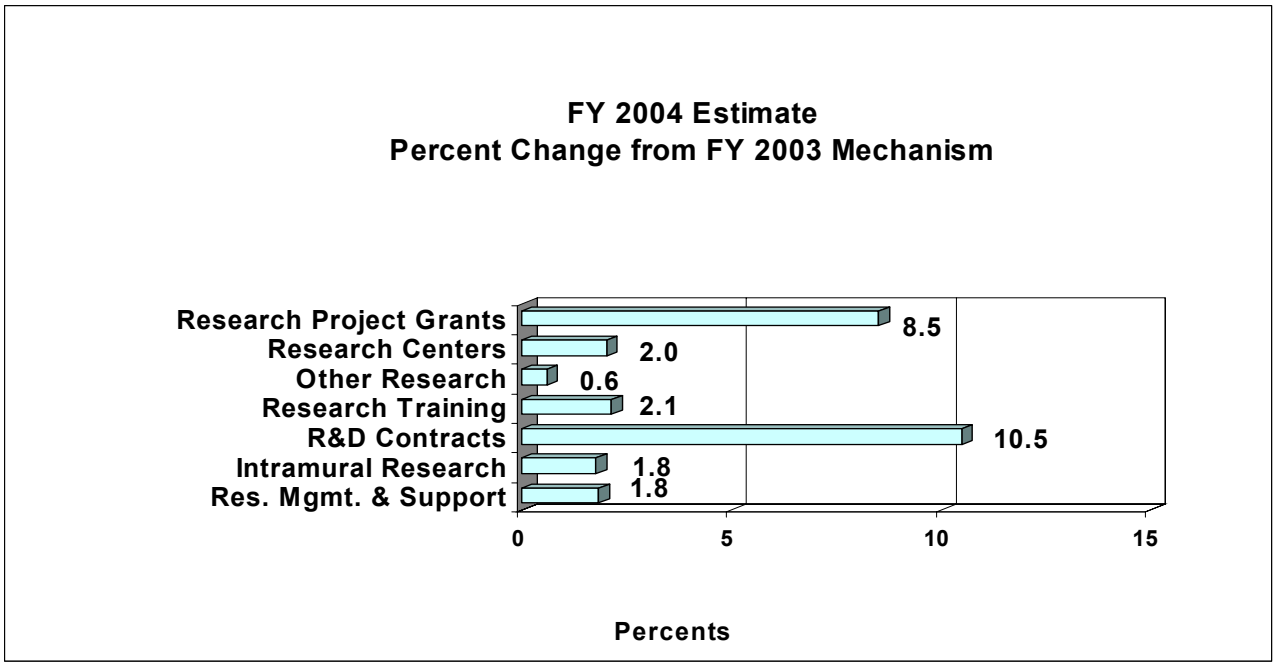
Also in FY 2004, NIDDK will fully fund 19 Academic Research Enhancement Awards (AREA) and Exploratory / Developmental Grants. AREA grants support small scale research projects conducted by faculty primarily within baccalaureate degree-granting domestic institutions. Exploratory / Developmental Grants are used to provide the development of new research activities in categorical program areas.

Promises for advancement in medical research are dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2004 request, NIDDK will support 980 pre- and postdoctoral trainees in full-time training positions, the same number as in FY 2003. Stipend levels for NRSA trainees will increase by 4 percent over Fiscal Year 2003 levels for predoctoral fellows, and from one to four percent, based on years of experience, for postdoctoral fellows.

The Fiscal Year 2004 request includes funding for 80 research centers, 530 other research grants, including 439 research career awards, and 324 R&D contracts. Intramural Research and Research Management and Support receive increases of 1.8 percent over FY 2003.

The mechanism distribution by dollars and percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism - Total

MECHANISM	FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	2,078	$735,199,000	2,278	$823,423,000	2,494	$911,018,000
Administrative supplements	(321)	50,955,000	(150)	10,500,000	(150)	10,500,000
Full funded	0	0	0	0	19	3,909,000
Single year	829	285,645,000	969	327,979,000	994	330,365,000
Subtotal, competing	829	285,645,000	969	327,979,000	1,013	334,274,000
Subtotal, RPGs	2,907	1,071,799,000	3,247	1,161,902,000	3,507	1,255,792,000
SBIR/STTR	121	34,681,000	118	33,767,000	144	41,700,000
Subtotal, RPGs	3,028	1,106,480,000	3,365	1,195,669,000	3,651	1,297,492,000
Research Centers:						
Specialized/comprehensive	69	78,986,000	71	86,842,000	71	88,580,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	2,260,000	9	1,695,000	9	1,750,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	69	81,246,000	80	88,537,000	80	90,330,000
Other Research:						
Research careers	388	47,493,000	439	56,126,000	439	56,126,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	3,809,000	7	3,741,000	7	3,750,000
Biomedical research support	0	1,452,000	0	0	0	0
Minority biomedical research support	0	2,415,000	0	2,415,000	0	2,415,000
Other	72	21,346,000	82	26,646,000	84	27,180,000
Subtotal, Other Research	460	76,515,000	528	88,928,000	530	89,471,000
Total Research Grants	3,557	1,264,241,000	3,973	1,373,134,000	4,261	1,477,293,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	152	6,697,000	157	7,107,000	157	7,320,000
Institutional awards	928	41,005,000	823	43,634,000	823	44,507,000
Total, Training	1,080	47,702,000	980	50,741,000	980	51,827,000
Research & development contracts	202	60,722,000	317	75,667,000	324	83,617,000
(SBIR/STTR)	(2)	(750,000)	(4)	(2,000,000)	(0)	(2,000,000)
	FTEs		FTEs		FTEs	
Intramural research	457	141,125,000	444	153,665,000	433	156,400,000
Research management and support	204	45,793,000	221	49,954,000	221	50,870,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NIDDK Program Level	661	1,559,583,000	665	1,703,161,000	654	1,820,007,000
(Clinical Trials)		(183,546,000)		(190,000,000)		(195,000,000)
Type One Diabetes Funds		(97,000,000)		(100,000,000)		(150,000,000)
Total, NIDDK Request		1,462,583,000		1,603,161,000		1,670,007,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2002 Actual FTEs	FY 2002 Actual Amount	FY 2003 Amended President's Budget FTEs	FY 2003 Amended President's Budget Amount	FY 2004 Estimate FTEs	FY 2004 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Division of Diabetes, Endocrinology and Metabolic Diseases		$647,665		$705,122		$778,891		$73,769
Division of Digestive Diseases and Nutrition		350,000		383,224		409,608		26,384
Division of Kidney, Urologic and Hematologic Diseases		375,000		411,196		424,238		13,042
Subtotal, Extramural research		1,372,665		1,499,542		1,612,737		113,195
Intramural research	457	141,125	444	153,665	433	156,400	(11)	2,735
Res. management & support	204	45,793	221	49,954	221	50,870	0	916
Total, Program Level	661	1,559,583	665	1,703,161	654	1,820,007	(11)	116,846
Type One Diabetes		(97,000)		(100,000)		(150,000)		
Total, NIDDK Request		1,462,583		1,603,161		1,670,007		66,846

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes				
2003 Amended President's Budget				$1,703,161,000
2004 Estimated Budget Authority				1,820,007,000
Net change				116,846,000
	2003 Amended President's Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$53,385,000		$754,000
b. Annualization of January 2003 pay increase		53,385,000		414,000
c. January 2004 pay increase		53,385,000		801,000
d. One extra day of pay		53,385,000		205,000
e. Payment for centrally furnished services		26,833,000		537,000
f. Increased cost of laboratory supplies, materials, and other expenses		73,447,000		1,189,000
Subtotal				3,900,000
2. Research Management and Support:				
a. Within grade increase		21,175,000		299,000
b. Annualization of January 2003 pay increase		21,175,000		164,000
c. January 2004 pay increase		21,175,000		318,000
d. One extra day of pay		21,175,000		82,000
e. Payment for centrally furnished services		6,229,000		125,000
f. Increased cost of laboratory supplies, materials, and other expenses		22,550,000		541,000
Subtotal				1,529,000
Subtotal, Built-in				5,429,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes--continued

CHANGES	2003 Amended President's Budget Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,278	$833,923,000	216	$87,595,000
b. Competing	969	327,979,000	44	6,295,000
c. SBIR/STTR	118	33,767,000	26	7,933,000
Total	3,365	1,195,669,000	286	101,823,000
2. Research centers	80	88,537,000	0	1,793,000
3. Other research	528	88,928,000	2	543,000
4. Research training	980	50,741,000	0	1,086,000
5. Research and development contracts	317	75,667,000	324	7,950,000
Subtotal, extramural				113,195,000
	FTEs		FTEs	
6. Intramural research	444	153,665,000	(11)	-1,165,000
7. Research management and support	221	49,954,000	0	-613,000
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
Subtotal, program		1,653,207,000		111,417,000
Total, Program Level Changes	665		(11)	116,846,000
Type One Diabetes				-50000
Total, NIDDK Request Changes				116,796,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Salaries and Expenses

OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$28,000,000	$28,780,000	$780,000
Other Than Full-Time Permanent (11.3)	20,875,000	21,490,000	615,000
Other Personnel Compensation (11.5)	980,000	1,000,000	20,000
Military Personnel (11.7)	1,180,000	1,210,000	30,000
Special Personnel Services Payments (11.8)	10,140,000	10,400,000	260,000
Total Personnel Compensation (11.9)	**61,175,000**	**62,880,000**	**1,705,000**
Civilian Personnel Benefits (12.1)	12,808,000	13,150,000	342,000
Military Personnel Benefits (12.2)	577,000	590,000	13,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**74,560,000**	**76,620,000**	**2,060,000**
Travel (21.0)	2,330,000	2,423,000	93,000
Transportation of Things (22.0)	570,000	593,000	23,000
Rental Payments to Others (23.2)	0	0	0
Communications, Utilities and Miscellaneous Charges (23.3)	1,180,000	1,230,000	50,000
Printing and Reproduction (24.0)	1,170,000	1,220,000	50,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	2,830,000	2,945,000	115,000
Other Services (25.2)	9,907,000	10,305,000	398,000
Purchases from Govt. Accounts (25.3)	51,510,000	53,596,000	2,086,000
Operation & Maintenance of Facilities (25.4)	4,475,000	4,660,000	185,000
Operation & Maintenance of Equipment (25.7)	2,060,000	2,145,000	85,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**70,782,000**	**73,651,000**	**2,869,000**
Supplies and Materials (26.0)	15,020,000	15,634,000	614,000
Subtotal, Non-Pay Costs	91,052,000	94,751,000	3,699,000
Total, Program Level Administrative Costs	**165,612,000**	**171,371,000**	**5,759,000**
Type One Diabetes	**(150000)**	**(150000)**	**0**
Total, NIDDK Administrative Costs	**165,462,000**	**171,221,000**	**5,759,000**

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Object

	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	665	654	(11)
Full-time equivalent of overtime & holiday hours	2	2	0
Average ES salary	$138,200	$142,070	$3,870
Average GM/GS grade	12.8	12.9	0.1
Average GM/GS salary	$88,773	$91,259	$2,486
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$71,019	$73,008	$1,989
Average salary of ungraded positions	113,475	$116,652	3,177
OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$28,000,000	$28,780,000	$780,000
11.3 Other than Full-Time Permanent	20,875,000	21,490,000	615,000
11.5 Other Personnel Compensation	980,000	1,000,000	20,000
11.7 Military Personnel	1,180,000	1,210,000	30,000
11.8 Special Personnel Services Payments	10,140,000	10,400,000	260,000
Total, Personnel Compensation	61,175,000	62,880,000	1,705,000
12.1 Civilian Personnel Benefits	12,808,000	13,150,000	342,000
12.2 Military Personnel Benefits	577,000	590,000	13,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**74,560,000**	**76,620,000**	**2,060,000**
21.0 Travel & Transportation of Persons	2,330,000	2,423,000	93,000
22.0 Transportation of Things	570,000	593,000	23,000
23.1 Rental Payments to GSA	10,000	10,000	0
23.2 Rental Payments to Others	0	0	0
23.3 Communications, Utilities & Miscellaneous Charges	1,180,000	1,230,000	50,000
24.0 Printing & Reproduction	1,170,000	1,220,000	50,000
25.1 Consulting Services	2,888,000	3,005,000	117,000
25.2 Other Services	9,907,000	10,305,000	398,000
25.3 Purchase of Goods & Services from Government Accounts	109,734,000	113,285,000	3,551,000
25.4 Operation & Maintenance of Facilities	4,475,000	4,660,000	185,000
25.5 Research & Development Contracts	61,348,000	69,298,000	7,950,000
25.6 Medical Care	875,000	910,000	35,000
25.7 Operation & Maintenance of Equipment	2,060,000	2,145,000	85,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**191,287,000**	**203,608,000**	**12,321,000**
26.0 Supplies & Materials	15,075,000	15,690,000	615,000
31.0 Equipment	11,000,000	11,450,000	450,000
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	1,405,965,000	1,507,148,000	101,183,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	14,000	15,000	1,000
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**1,628,601,000**	**1,743,387,000**	**114,786,000**
Total, Budget Authority by Object	**1,703,161,000**	**1,820,007,000**	**116,846,000**
Type One Diabetes	**(100,000,000)**	**(150,000,000)**	
Total, NIDDK Request	**1,603,161,000**	**1,670,007,000**	**66,846,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN SENATE APPROPRIATIONS COMMITTEE REPORT

The following section represents FY 2003 Congressional requirements for reports and significant items derived from Senate Report 107-216. These actions discussed below are contingent on inclusion of similar language and funding in the final FY 2003 appropriation and related reports. Additional items may be transmitted at a later date as a result of the final Conference report.

Item

[Behavioral research] – Depression has been linked to poorer adherence to medical and behavioral regimens and lower rates of exercise. The Committee also notes that a recent NIDDK clinical trial on diabetes, the Diabetes Prevention Program, demonstrated that diet and exercise could be more successful than medication in preventing the development of diabetes in groups that faced a high risk of diabetes. The NIDDK is strongly encouraged to build on its investment in behavioral research, particularly in areas that would add to the science base on the maintenance of positive behavior change. **(Page 108)**

Action Taken or to be Taken

People with diabetes have twice the rate of depression seen in the general population. Moreover, people with depression have an increased prevalence of diabetes. A conference sponsored in January 2001 by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Mental Health, and the NIH Office of Behavioral and Social Sciences Research (OBSSR), focused on research issues in depression in diabetes and other selected chronic diseases. This was followed by a solicitation to address specific research issues identified in the conference and to increase research on the relationships among depression, eating disorders, diabetes, and obesity, and to explore how treatment of psychological disorders may improve outcomes in diabetes. As a follow-up to the conference, NIDDK scientists have analyzed data on diabetes and depression from the National Health and Nutrition Examination Survey and will soon release a publication detailing this analysis. The NIDDK, along with the National Eye Institute, the National Institute of Nursing Research (NINR), the NIH Office of Behavioral and Social Sciences Research, the Agency for Healthcare Research and Quality, and the Centers for Disease Control and Prevention, recently issued a solicitation to encourage translational research for the prevention and control of diabetes. A trans-NIH obesity initiative, sponsored by the NIDDK; the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute on Aging; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the National Institute of Child Health and Human Development; and the National Institute of Nursing Research, will address the relationship between obesity and physical activity. Both of these initiatives will encourage positive behavior change to improve health.

The landmark Diabetes Prevention Program (DPP) clinical trial, completed in 2001, showed that a five to seven percent reduction in body weight and 30 minutes of exercise at least five times a week cut the risk of developing type 2 diabetes by 58 percent in individuals at high risk for developing the disease. This "intensive lifestyle intervention" was highly effective for both genders and all ages and racial/ethnic groups in the study. Much of the success of the DPP derives from the strong knowledge base gained from several decades of investment in basic behavioral intervention research and the translation of that research. To help achieve the goals of the intensive lifestyle intervention, participants were seen individually and received ongoing intervention throughout the trial. All individuals initially participated in a 16-session core curriculum that taught basic information about nutrition, physical activity, and behavior change. A "tool box" of approaches was used to allow for individualization of the intervention. In addition, there was flexibility in the delivery of the intervention for an ethnically diverse population. The DPP centers also offered group courses and motivational campaigns during the trial. The DPP also included assessments of depression periodically over the course of the study. These data are currently being analyzed to answer a key question regarding the association of diabetes and depression identified at the January 2001 conference previously mentioned. Specifically, it is hoped that these data will help to determine whether diabetes increases the risk of depression, or whether depression increases the risk of diabetes. Long-term follow-up studies are under way to assess the durability of the DPP interventions in preventing or delaying diabetes, and to determine whether the interventions reduce cardiovascular disease and atherosclerosis, major causes of death in people with type 2 diabetes.

Item

Children and adolescent urological diseases **–** While research on urologic diseases has led to advances in the care and management of some urologic diseases affecting adults, these diseases persist as a major cause of illness among the most vulnerable population, children and adolescents. The NIDDK should develop and implement an interagency plan for pediatric urologic disease research. The Committee requests the NIDDK to submit a status report prior to the fiscal year 2004 appropriations hearings that outlines the steps it is taking to address the specific research needs of children and adolescents suffering from urologic diseases and conditions. **(Pages 108-109)**

Action Taken or to be Taken

Genitourinary birth defects are among the most common congenital abnormalities in newborns. Many congenital defects in the bladder and urinary tract can have immediate life-threatening consequences to the newborn or long-term effects on proper bladder and kidney function. The NIDDK has taken several steps to plan and implement research efforts that address urological diseases in children. First, the Bladder Research Progress Review Group (PRG) convened by the NIDDK devoted a chapter of their recently issued report on the state of bladder research to problems of the developing genitourinary tract – not the bladder exclusively – in children. In addition to presenting background information on pediatric genitourinary diseases and current research, the report identifies particular research opportunities and requirements and research recommendations for specific urological conditions affecting children and adolescents. Thus, this report will serve as a crucial guide for the NIDDK's current and future plans for urology research targeting these conditions.

Second, the NIDDK continues to solicit external expertise in its planning process for research on urological diseases in children through timely meetings and workshops. In cooperation with the American Society for Pediatric Nephrology, the Society for Pediatric Urology, the National Kidney Foundation, and the American Academy of Pediatrics Section on Urology, the NIDDK planned and sponsored the two-day "Congenital Urinary Tract Obstruction: A State of the Art Strategic Planning Workshop," held in March 2002. Experts from the fields of nephrology, urology, pediatrics, perinatology, embryology, and genetics reviewed basic and clinical knowledge of urinary reflux and obstructive uropathy in children, determined areas where additional basic and clinical research is needed, and drafted recommendations for future research; the meeting report is available for download at (http://www.niddk.nih.gov/fund/other/pediatric.pdf). These recommendations will be invaluable in NIDDK's planning process for future initiatives in this area.

Third, anatomic disorders of the urinary tract are a leading cause of kidney disease in children. Thus, studies of pediatric kidney disease overlap with studies of pediatric urological disorders. In response to recommendations emanating from the April 2002 meeting of its Task Force on Chronic Kidney Disease in Children, the NIDDK, in collaboration with the National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological Disorders and Stroke (NINDS), has issued a research solicitation to establish a long-term prospective cohort study of kidney disease in children. It is anticipated that approximately 40 percent of children recruited for this study will have anatomic disorders of the urinary tract. These disorders – and their contributions to pediatric chronic kidney disease and its effects on childhood development and adult risk for cardiovascular disease – are to be addressed in the planned cohort study. A recent advisory meeting for development of this pediatric cohort study also included review of recommendations from the March workshop on Congenital Urinary Tract Obstruction.

Finally, to further galvanize research in pediatric urological diseases, the Kidney, Urology, and Hematology Interagency Coordinating Committee, led by NIDDK, plans to focus on this topic at its Spring 2003 meeting. Based upon the outcome of discussions at this meeting, a strategic planning process to address pediatric kidney and urological diseases can then be developed.

Item

Chronic prostatitis **–** The Committee requests that the NIDDK increase funding for the Chronic Prostatitis Collaborative Research Network. The Institute is also encouraged to stimulate new and diverse research in chronic prostatitis by convening a scientific and clinical workshop to be held in fiscal year 2003 which will disseminate the findings of the CPCRN and develop a strategic research plan. **(Page 109)**

Action Taken or to be Taken

The NIDDK established the Chronic Prostatitis Collaborative Research Network (CPCRN) in 1997 to conduct epidemiological studies and clinical trials in men with chronic prostatitis. The Network, which consists of 10 clinical centers and a data coordinating center, first undertook a prospective study of nearly 500 men with symptoms of the disorder who could be followed over time and compared with an age matched, "control" group of men. Data obtained from this cohort was used

to gain further insights into the characteristics of men with chronic prostatitis. Subsequently, the Network initiated the first of several clinical trials to evaluate the effects of various therapies on the symptoms of the disease. The first randomized, placebo-controlled clinical trial of therapy using the alpha blocker tamsulosin and an antibiotic was initiated in 2001. It is anticipated that this trial, and data analysis, will be completed in the spring of 2003.

In FY 2003, the Institute is re-competing awards for the Network for a second five-year period, during which the Network will continue to plan and conduct randomized clinical trials to evaluate novel therapies in patients with chronic prostatitis. In addition, in FY 2003 the Institute plans to convene a scientific workshop that will present results to date of the Network project, including the trial and data from the long-term follow-up of the cohort, and some scientific reports from ancillary studies, as well as identify potential areas for future research.

Item

Diabetes in Native Hawaiians – The Committee encourages the NIDDK to investigate the incidence of diabetes in Native American, Hawaiian, and Alaskan populations, as well as the Mississippi Band of the Choctaw Indians and the Eastern Band of the Cherokee Indians. **(Page 109)**

Action Taken or to be Taken

In September 2002, the NIDDK collaborated with the National Institute of Neurological Disorders and Stroke (NINDS), the National Eye Institute (NEI), the National Institute of Nursing Research (NINR), and the National Heart, Lung, and Blood Institute (NHLBI) to issue a Program Announcement (PA) to support research to address the underlying metabolic and physiologic mechanisms that contribute to the racial and ethnic differences in the incidence of type 2 diabetes and its devastating complications. The NIDDK supports the Centers for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES), which will help to shed light on the prevalence of diabetes in minority populations, including American Indians, Native Hawaiians, and Alaskan populations. The Institute is also cosponsoring a CDC effort entitled "Search for Diabetes in Youth," to address the incidence of diabetes in a multi-ethnic pediatric population, which includes a Hawaiian site. In addition to assessing the incidence of diabetes in these populations, the NIDDK is also funding research aimed at the discovery of ways to intervene and prevent development of diabetes.

The NIDDK is supporting faculty at tribal colleges and universities as they develop science education programs targeted at tribal community middle and high schools. The objective of this effort is to both increase knowledge of diabetes and to encourage American Indian students to pursue careers in biomedicine. The NIDDK also works to increase awareness and knowledge about diabetes through its support of the National Diabetes Education Program (NDEP). The NDEP is a collaborative initiative of the NIH and the CDC that involves over 200 public and private partnerships to promote, through education, the clinical application of the therapies and other approaches that have demonstrated value in the prevention of type 2 diabetes and diabetic complications. A key feature of this program is the participation of individuals who represent communities such as African Americans, Hispanics/Latinos, American Indians, Alaska Natives, and Asian and Pacific Islanders, who are disproportionately affected by type 2 diabetes.

In August 2001, the NIDDK and other sponsoring Health and Human Services (HHS) institutes and agencies announced the exciting results of a major long-term clinical trial, the Diabetes Prevention Program (DPP). This trial demonstrated that, in those at highest risk for developing type 2 diabetes, a lifestyle intervention consisting of weight loss and exercise could reduce the incidence of diabetes by 58 percent, and a drug intervention could reduce disease onset by 31 percent. The DPP randomized over 3,200 individuals to its three-arm study (lifestyle intervention, drug treatment, and control groups.) All racial and ethnic groups receiving the lifestyle intervention, including 142 American Indians and 20 Native Hawaiians, demonstrated a decrease in development of type 2 diabetes.

Former DPP participants are now being followed in the post-DPP study, the DPP Outcomes Study (DPPOS). All persons in the cohort who consent to continued inclusion will be tested for development of type 2 diabetes, as well as for microvascular, macrovascular, and behavioral effects of diabetes.

Item

Digestive diseases – Diseases of the digestive system, such as colorectal cancer, inflammatory bowel disease, irritable bowel syndrome, hemochromatosis, celiac disease, and hepatitis, affect more than one-half of all Americans at some time in their lives. The Committee commends the NIDDK on the success of its Digestive Disease Centers program in addressing a wide range of disorders that result in tremendous human suffering and economic cost. The Committee encourages the Institute to expand this program. **(Page 109)**

Action Taken or to be Taken

The NIDDK continues to support and expand the Digestive Disease Research Core Centers (DDRCC) program. The goal of this program is to foster research, collaborations, and new directions in digestive and liver research. The number of centers has increased over the past three years from 12 to a current total of 16. The centers cover a broad range of diseases, including liver disease, inflammatory bowel disease, and other digestive diseases.

The NIDDK issued a Request for Applications for Digestive Diseases Research Development Centers in April 2001. These will be "mini" centers that will support shared research resources, or cores, to be used by groups of NIDDK-funded investigators who do not have access to one of the large DDRCC's. The "mini" centers will focus on important issues in gastrointestinal (GI) diseases that may not be adequately represented in the large centers, such as pediatric liver disease, irritable bowel syndrome, pancreatic disease, gene therapy, stem cell biology in the adult liver and GI tract, and GI AIDS. The availability of these resources will enhance capabilities for conducting basic, clinical, and/or translational digestive diseases research. The centers will be funded in FY 2003.

Item

Glomerular injury research – The Committee is pleased with the NIDDK's glomerular injury research initiatives, including a clinical trial for patients with focal segmental glomerulosclerosis. Further, the Committee continues to encourage the NIDDK to consider initiating a scientific conference on glomerular injury research, and to explore support for gathering prevalence data on glomerular injury. **(Page 109)**

Action Taken or to be Taken

As part of the NIDDK-funded trial of therapy for glomerular injury, a consortium of four centers has begun to develop a protocol to study treatments for children and young adults with focal segmental glomerulosclerosis (FSGS). This disease, which causes leakage of protein into the urine (a condition known as proteinuria), is relatively common in these age groups, causes kidney failure in many cases, and has been highly resistant to therapy.

Excessive amounts of protein in the urine are associated with kidney damage and risk of developing progressive kidney failure. Because of the importance of proteinuria and its value as a marker for kidney disease, in October 2002, the NIDDK and the National Kidney Foundation sponsored a meeting entitled "Proteinuria and Other Markers of Chronic Kidney Disease: Perspectives on Clinical Practice, Trials, and Research Needs." Topics discussed at the meeting included Population Measures of Proteinuria, and Testing Proteinuria in Children, Proteinuria as a Predictor of Outcome and Response Therapy, and other subjects of research importance.

Item

Hematology – The Committee is aware of the high-quality hematology research in iron metabolism, gene regulation, and stem cell plasticity currently funded by the Institute, and it encourages the NIDDK to plan the next steps in setting priorities for future research in these and other areas that significantly impact a broad array of blood disorders. **(Page 109)**

Action Taken or to be Taken

The NIDDK has taken a number of steps to plan and establish research activities that will significantly enhance knowledge and treatment of blood disorders. In response to recommendations developed at a recent workshop, the NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) anticipate initiating new research grants to medical and small business institutions for projects that may improve the utility of magnetic resonance imaging as a method for quantitative determinations of body iron. Magnetic resonance imaging potentially provides a useful and widely available technique for monitoring excess iron in the body in conditions of iron overload, such as found in thalassemia (Cooley's anemia) and sickle cell disease patients.

The Institute has also sought expert input on the state of research on the biological basis of iron overload disorders. The NIDDK and the National Heart, Lung, and Blood Institute (NHLBI) recently organized a meeting of grantees from several Requests for Applications (RFAs) related to iron metabolism and iron overload, in order to monitor progress on these projects and to determine

areas needing additional research efforts. Rapid progress continues to be made in identifying factors involved in the regulation of iron metabolism pathways that ultimately may prove useful as clinical management tools. Currently, follow-up studies are planned as a result of NIDDK-supported research showing a much lower than anticipated incidence of clinical disease symptoms among carriers of the most common gene mutation for hereditary hemochromatosis. Such studies may elucidate additional factors that influence how the body processes excess iron.

Facilitating future research on blood cell development and blood disorders, the Institute has initiated a Consortium of Genome Anatomy Projects (GAPs), involving eminent groups of hematopoietic stem cell investigators. These stem cell GAPS are aimed at developing the necessary biological procedures and reagents for characterization of cells of the hematopoietic lineage and characterizing gene expression patterns in these cells using advanced technologies and bioinformatics techniques. These projects will interact closely with similar projects related to bone, liver, intestine, kidney, and pancreatic cell development, with the promise for novel approaches to the study of pathogenesis and treatment of human diseases. As these projects yield information, additional studies will be possible to identify proteins and other factors involved in maintenance of health and the pathogenesis of disease.

The NIDDK has funded a large number of projects to examine the complex issues related to reported adult stem cell plasticity. A recent meeting of grantees, funded by the NIDDK, NHLBI and National Institute of Neurological Disorders and Stroke (NINDS), examined developments in this area, and the research issues raised by recent reports in the literature. As a result of the meeting, new efforts are being made to resolve scientific issues, and to examine the clinical applicability of the reported plasticity.

Item

Hepatitis C – The Committee remains concerned about the disproportionate impact of hepatitis C among minorities. The Committee encourages the NIDDK to expand research on better treatment options for minorities, and to partner with the CDC and voluntary health organizations to facilitate a prevention and education campaign targeted at high-risk populations. **(Page 109)**

Action Taken or to be Taken

The NIDDK is addressing the disproportionate impact of hepatitis C among minorities through an initiative entitled, "Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C)." This initiative will establish a multicenter clinical trial dedicated to investigating viral resistance to interferon alpha therapy in patients with chronic hepatitis C. The study is focusing on African Americans, who are disproportionately resistant to this therapy. Long-term response rates to combinational antiviral therapy of hepatitis C among African Americans will be compared to non-Hispanic whites. Four hundred patients– African Americans and Caucasians– who are infected with the hepatitis C virus strain predominantly linked to viral resistance, will be treated with pegylated interferon plus the antiviral drug ribavirin. During treatment, the patients will be followed intensively for differences in response to therapy. The trial supports one coordinating center and eight clinical centers. In addition, four ancillary studies are being funded to investigate the role of patient genetics, viral genetics, patient metabolic response to interferon, and patient immune

response to the hepatitis C virus. A Cooperative Research and Development Agreement with a major pharmaceutical company was finalized in July 2002. In July 2002, the first patient was screened for the trial and in September 2002, the first patient was enrolled in the study.

The NIDDK is in the preliminary stages of planning a website dedicated to hepatitis. The site will target three audiences: the public, scientists, and clinicians. Information for the public will consist mainly of links to other existing web resources such as the NIDDK, the National Institute of Allergy and Infectious Diseases, and the Centers for Disease Control and Prevention (CDC). For scientists, the focus will be on promoting research in the field of hepatitis. Information will be posted on research training and grantsmanship, grant listings, career development, conferences and workshops, and other important topics. For clinicians, there will be information on clinical trials and other clinical research. The site will be hosted and maintained by the NIDDK. A website (http://www.hepatitis.nih.gov) is already reserved for this project.

The NIDDK and the CDC collaborated to plan a January 2003 meeting entitled "Hepatitis C in Correctional Institutions," because the correctional institution population is at high risk for hepatitis C. The NIDDK and the CDC also co-fund a study of chronic liver disease in the U. S. that provides important information on the rates of liver disease in different ethnic and racial groups by age and gender, and the changes in these rates over time.

Item

Inflammatory bowel disease – The Committee has been encouraged in recent years by discoveries related to Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel disease (IBD). These extremely complex disorders represent the major cause of morbidity and mortality from intestinal illness. The Committee commends NIDDK for its strong leadership in this area and encourages the Institute to continue to give priority consideration to the following areas of IBD research: (1) investigation into the cellular, molecular and genetic structure of IBD, (2) identification of the genes that determine susceptibility or resistance to IBD in various patient subgroups, and (3) coordination and integration of basic investigations designed to clarify mechanisms of action and disease pathogenesis into clinical trials. **(Page 110)**

Action Taken or to be Taken

The NIDDK will bolster its strong basic and clinical research portfolio in IBD with the funding of a new Inflammatory Bowel Disease Genetics Research Consortium. The Consortium, funded as a result of a Request for Applications (RFA) issued in FY 2001, will aim to identify genes or genomic regions associated with increased risk of developing IBD and with specific clinical manifestations, such as age of onset, response to therapy, or susceptibility to environmental risk factors. These efforts will build upon the recent major discovery, supported by the NIH, of the first susceptibility gene for Crohn's disease, *Nod2* (also called *Card15*). It is anticipated that the Consortium will foster collaborative interactions among scientists, encourage novel approaches towards identifying genes that contribute to IBD, and create resources for genetic studies. The Consortium's long-term goal is to increase molecular understanding of IBD so as to open new avenues of research towards the development of novel therapies and new diagnostic methods. The NIDDK will also continue funding its Digestive Diseases Research Centers, including support for centers that focus on IBD

research, and research training in this area. Further, the NIDDK planned a January, 2003 workshop to discuss endpoints for clinical research in inflammatory bowel diseases. In other areas relevant to IBD, the Institute will support studies on progenitor cells of the gut and research relating to potential autoimmune and microbial influences in the development of IBD. Additionally, as IBD and other diseases may necessitate surgical removal of large portions of the bowel, resulting in short gut syndrome, the NIDDK recently published a Program Announcement (PA) to encourage basic and clinical research into intestinal failure, short gut syndrome and intestinal transplantation.

Item

Interstitial cystitis – The Committee is very concerned by the direction of interstitial cystitis (IC) research at the NIDDK in the last two budget cycles. Despite strong congressional interest in expanding such research, the NIDDK did not invest in new IC-specific research grants during fiscal year 2002 and has thus far not committed to doing so in fiscal year 2003. The Committee urges the NIDDK to reverse this trend and aggressively support research that will enhance the basic science knowledge of IC through IC-specific research. **(Page 110)**

Action Taken or to be Taken

Interstitial cystitis (IC) is a serious, chronic, and disabling bladder disease that primarily affects women. The NIDDK, the only NIH Institute supporting research on IC, is committed to research to combat this disease. In FY 2002, the NIDDK co-funded three Specialized Centers of Research with the Office of Research on Women's Health (ORWH). These centers will address: (1) urinary incontinence; (2) urinary tract infections; and (3) IC and Irritable Bowel Syndrome (IBS), two conditions which often occur in the same individual. The third center will conduct both clinical research studies in patients with IC and IBS, and basic research studies using animal models of IC and IBS.

For FY 2003 and beyond, the NIDDK has already planned several initiatives to promote basic and clinical research on or relevant to IC. The NIDDK has drafted two new solicitations for bladder research for release later in FY 2003. The NIDDK expects to issue a Request for Applications (RFA) on "Basic Research Related to Interstitial Cystitis (IC)," and a Program Announcement to solicit proposals for "Basic Research Studies on the Biology of the Bladder." To facilitate full funding of the IC basic research RFA once it has been issued, the NIDDK has posted a description of the incipient RFA on its website for potential applicants to review, and the Institute and the Interstitial Cystitis Association (ICA) are cooperating to publicize the upcoming availability of this RFA through multiple channels. Through these efforts to increase visibility for the RFA, the NIDDK hopes to receive a similarly strong response from the existing IC research community and to attract applications from investigators new to the field. The NIDDK has set aside several million dollars of its anticipated FY 2003 appropriation to fund this RFA; as with other NIH research solicitations, the final amount of funds awarded through this RFA will depend upon the number of scientifically meritorious applications received.

Item

[ICCTG Centers] – The Committee is pleased that NIDDK has pledged continued support and expansion of the IC Clinical Trials Group. The Committee is aware that the group is making good progress on the evaluation of BCG for the treatment of IC. Ancillary studies, including urinary marker studies, are being done concurrently, and will help provide an understanding of the differences between responders and non-responders. The Committee feels strongly that funding for ancillary studies should be included in the recompetition of the RFA for the ICCTG clinical centers. This will ensure peer review, and at the same time, avoid possible significant delays in funding of the ancillary studies should they be offered through a different mechanism. **(Page 110)**

Action Taken or to be Taken

The NIDDK expects to maintain and expand upon its clinical research efforts to combat IC through its recently issued RFA, "Interstitial Cystitis Clinical Research Network (ICCRN)." This RFA is a recompetition and expansion of the IC Clinical Trials Group established by the NIDDK through an RFA issued in 1997. The NIDDK hopes to fund a second five-year clinical trials group, with enhanced opportunities to develop ancillary studies in conjunction with the clinical trials; the development of these ancillary studies is a specific goal of the RFA. Because the current ICCTG data coordinating center is very strong scientifically and has a substantial data and specimen bank, the NIDDK is specifically inviting the current site to submit a request for continuation through a letter RFA. Through successful recompetition of this RFA, the NIDDK expects that the current ICCTG will be able to continue smoothly with the kinds of studies it is presently pursuing, and, with the addition of ancillary studies, the NIDDK will be positioned to translate any new research advances that emerge from its basic bladder research portfolio into new clinical interventions. This program should thus aid in the scientific assessment of potential new treatments for IC that could have a direct, beneficial impact on patient care.

Item

[Bladder Research Review Group Recommendations] – The Committee is also pleased that the NIDDK completed a draft of the recommendations put forth by the Bladder Research Review Group and will issue its final report in 2002. The Committee urges that the strategic plan's recommendations regarding IC be implemented and fully funded as soon as possible. The Committee requests a full update on this and all IC-related research activities as part of the NIDDK's written testimony for the fiscal year 2004 Senate appropriations hearing. **(Page 110)**

Action Taken or to be Taken

The Bladder Research Progress Review Group (PRG) has issued its final report evaluating the state of bladder research and recommending specific ways to improve research on the bladder and on bladder diseases, including IC. Based upon these recommendations, and with input from the Interstitial Cystitis Association (ICA), the NIDDK has drafted two new solicitations for bladder research for release later in FY 2003. The NIDDK expects to issue a Request for Applications (RFA) on "Basic Research Related to Interstitial Cystitis (IC)," and a Program Announcement to solicit proposals for "Basic Research Studies on the Biology of the Bladder."

Item

Irritable bowel syndrome – The Committee remains concerned about the increasing frequency of irritable bowel syndrome (IBS), and it encourages NIDDK to partner with other Institutes and Centers to enhance research on this disorder, including studies on its prevalence. **(Page 110)**

Action Taken or to be Taken

To strengthen research on IBS, the NIDDK has partnered with the NIH Office of Research on Women's Health to co-fund a new Specialized Center of Research (SCOR). Research at this SCOR will focus on the role of the brain, stress, and emotions in disorders that primarily affect women, including irritable bowel syndrome. By drawing upon resources such as the Digestive Diseases Interagency Coordinating Committee (DDICC), which was statutorily-mandated to coordinate interagency assessment of needs and pursuit of research opportunities in digestive diseases, the NIDDK plans to pursue further research efforts in functional bowel disorders. These may include trans-agency efforts to facilitate studies on IBS prevalence, with disease surveillance encompassed within the mission of the Centers for Disease Control and Prevention, as well as other research on IBS.

Item

Islet cell transplantation – The Committee is pleased with NIH-supported research involving the transplantation of insulin-producing islet cells into individuals with juvenile diabetes. The Committee encourages the NIDDK to work closely with the NIAID on initiatives to create and maintain immune tolerance to transplanted islet cells. In addition, the Committee encourages the NIDDK to vigorously pursue all avenues of research that could lead to alternative supplies of insulin-producing cells, including stem cell technology. **(Page 110-111)**

Action Taken or to be Taken

With the recent achievement of promising results in islet transplantation research, the NIH has intensified support for such clinical studies and for alternative sources of insulin-producing cells. The NIDDK intramural program has initiated a series of islet transplant procedures in a small number of adult patients with severe type 1 diabetes. The NIDDK is co-sponsoring the Immune Tolerance Network (ITN), an initiative led by the National Institute of Allergy and Infectious Diseases, to perform multi-center clinical trials of islet transplantation and to begin clinical trials to evaluate potential tolerance approaches in human islet transplantation. Complementing these efforts, the NIDDK expanded regular research grant support to a range of independent investigators in the extramural community to hasten their work on islet transplant approaches. The NIDDK also increased support to its Diabetes and Endocrinology Research Centers to enhance islet encapsulation approaches as a method of preventing immune destruction of islets. The NIDDK has also established the Collaborative Islet Transplant Registry to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America.

Before islet transplantation could be offered to all who might benefit, the supply of islets would need to be greatly increased. The shortage of islets for transplantation could be addressed by coaxing stem cells to develop into insulin-secreting pancreatic beta cells. Based on recommendations of the Diabetes Research Working Group and two international workshops, the NIDDK has established consortia to facilitate progress in beta cell biology. The Functional Genomics of the Developing Endocrine Pancreas Consortium is generating important genomic and bioinformatics tools from studies of developing mouse and human pancreatic tissue. These tools are being made freely and rapidly available to the diabetes research community (http://www.cbil.upenn.edu). The Beta Cell Biology Consortium is developing new mouse models and research tools to investigate beta cell development and regeneration, and is exploring new ways of producing differentiated islet cell types from multiple mouse and human stem cell sources (www.betacell.org). These consortia are jointly assembling a public database that will permit rapid dissemination of data, which is expected to greatly stimulate research in this area.

Item

Juvenile diabetes **–** The Committee urges the NIDDK to continue development of a vaccine to prevent juvenile diabetes, and to collaborate with other Institutes on this project. In addition, the Committee commends the NIDDK for its efforts to determine the genetic origins of juvenile diabetes, including the development of a Type 1 Diabetes Genetics Consortium, which will collect and share valuable DNA information from juvenile diabetes patients from studies around the world. The Committee encourages the NIDDK to continue and expand this effort to determine the genetics of the complications of diabetes, such as retinopathy, kidney disease and neuropathy. The Committee also remains concerned about reports of a shortage of pediatric endocrinologists, and it urges the NIDDK to enhance efforts to address this serious problem. **(Page 111)**

Action Taken or to be Taken

Type 1 diabetes – also known as juvenile diabetes – is an "autoimmune" disease in which the body's immune defense system attacks and destroys the insulin producing cells of the pancreas. To facilitate clinical research on strategies to prevent or reverse this autoimmune process, the NIDDK has launched the Type 1 Diabetes TrialNet. This network of clinical centers, investigators, and core support facilities in the U.S. and Canada supports the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new-onset patients and to prevent type 1 diabetes in those at-risk of this disease. TrialNet, which comprises 14 clinical centers and approximately 350 recruitment sites, is co-sponsored with the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, American Diabetes Association (ADA), and Juvenile Diabetes Research Foundation International (JDRF). A number of potential new agents – including antigen and antibody-based therapies, and novel immunosuppressives – are in varying stages of development. The large-scale, collaborative nature of this clinical research network should accelerate the search for a vaccine or other strategy to prevent type 1 diabetes.

The Diabetes Control and Complications Trial (DCCT) showed that the development of diabetic complications – specifically, severe eye and kidney disease – is influenced by genetic factors. The NIDDK is pursuing two major research efforts to uncover the genetic bases of diabetic

complications. The Epidemiology of Diabetes Interventions and Complications Study (EDIC), the long-term follow-up of the DCCT, offers a unique opportunity to study complications because of the depth and breadth of clinical data on glucose control, other risk factors for diabetic complications, co-morbid conditions, genetic factors, and family history that have been collected in this type 1 diabetic cohort for nearly 20 years. Participation rates for these enthusiastic study volunteers remain near 95 percent. DNA and cell lines from over 1,400 DCCT/EDIC participants and their diabetic and non-diabetic relatives are being collected and analyzed to look for susceptibility genes for diabetes complications. In addition, the Family Investigation of Nephropathy and Diabetes (FIND) Study, which is co-sponsored with the National Eye Institute and the National Center on Minority Health and Health Disparities, is searching for genes involved in diabetic kidney and eye diseases. Six study centers will recruit a total of over 3,300 patients over three and a half years. In contrast to EDIC, FIND is investigating the genetic associations of complications in individuals with either type 1 or type 2 diabetes.

Management of diabetes in children is particularly arduous and requires an exceptional level of effort from the children, their families, and their health care providers. These extraordinary clinical care demands make it challenging for pediatric endocrinologists involved in diabetes care to also pursue research careers. The NIDDK, ADA, and JDRF are co-sponsoring programs of research training and career development in pediatric endocrinology. The training institutions have environments, mentors, and programs that will make them particularly effective in enhancing the number of independent investigators contributing to research in pediatric endocrinology.

Item

Kidney disease and end-stage renal disease – Diabetes is the leading cause of kidney failure and end-stage renal disease. The Committee urges the NIDDK to expand research into early prevention and therapeutic intervention of kidney disease to prevent end-stage renal failure. The Committee also encourages the NIDDK to consider launching a permanent kidney disease clinical research mechanism. Finally, the Institute is urged to address an anticipated workplace shortage in nephrology by launching new training initiatives and workshops to foster interest in the field. **(Page 111)**

Action Taken or to be Taken

In an effort to prevent the progression of kidney disease to end-stage renal disease, in March 2003, the pilot National Kidney Disease Education Program will launch a campaign to increase awareness of kidney disease among primary care providers and a high risk population – African Americans with diabetes, hypertension, and/or a family member with kidney failure. The educational messages will focus on identifying the risk factors for kidney disease, the importance of testing individuals found to be at risk, and providing appropriate treatment to those diagnosed with kidney disease.

In 2001, the African American Study of Kidney Disease and Hypertension (AASK) completed a successful study of blood pressure therapy in African Americans with hypertensive kidney disease. This group of study participants are now continuing in a study to learn more about the course of treated chronic kidney disease. Risks for progressive disease persist even in the face of therapy, and

this continued observation will aid in identifying these risk factors and determining whether they constitute new targets for prevention or therapy.

To promote further research into therapies for kidney disease, a Renal Trials Consortium is being established. The first meeting of the members of consortium will occur in February 2003. Funds have been designated for study design and statistical assistance for members to devise pilot and feasibility studies of clinical kidney disease. An NIDDK-wide repository for data and samples from all clinical trials will also facilitate these efforts and create greater value from these trials.

Although the NIDDK supports vigorous research training and career development programs and participates in the NIH Loan Repayment Program (which seeks to recruit and retain highly qualified health professionals in clinical and pediatric research through educational loan repayment), the Institute recognizes that additional efforts are necessary to foster interest in nephrology. In December 2002, the NIDDK sponsored its third annual workshop on "Preparing for a Career in Clinical and Genetic Research in Nephrology." This 2½-day workshop provided the opportunity for researchers to learn the skills needed to have a successful clinical research career and to effectively compete for research funding. The training program included lectures, mentored training sessions on clinical research and study design, manuscript and grant writing, and a mock study section.

Item

[Kidney disease research] **–** The Committee commends the NIDDK for its leadership in moving forward in this area, by holding an initial workshop to develop strategies that will strengthen kidney research and enhance researchers' abilities to translate research findings to the bedside, facilitate clinical trials, and recruit patients for studies. The Committee urges the NIDDK to continue with these efforts, and to make the necessary funds available in this fiscal year to launch a permanent kidney disease clinical research mechanism. **(Page 111)**

Action Taken or to be Taken

The NIDDK continues to support a robust and varied program of kidney disease clinical research. In 2001, the African American Study of Kidney Disease and Hypertension completed a successful study of blood pressure therapy in African Americans with hypertensive kidney disease. This group of study participants are now continuing in a study to learn more about the course of treated chronic kidney disease. Risks for progressive disease persist even in the face of therapy, and this continued observation will aid in identifying these risk factors and determining whether they constitute new targets for prevention or therapy.

A Renal Trials Consortium is being established. The first meeting of the members of the consortium will occur in February 2003. Funds have been designated for study design and statistical assistance for members to devise pilot and feasibility studies of clinical kidney disease. An NIDDK-wide repository for data and samples from all clinical trials will also facilitate these efforts and create greater research benefits from those trials.

The Chronic Renal Insufficiency Cohort study will begin to recruit participants in April 2003 after a year of intensive protocol design. The study will follow 3,000 individuals with chronic kidney disease who will not have reached kidney failure. The observation will last for seven years and will seek to determine the factors that contribute to a high risk for cardiovascular disease and a tendency to develop kidney failure among the participants. Patients with diabetes will make up one half of the cohort.

A consortium of four centers have begun to develop a protocol to study treatments for children and young adults with focal segmental glomerulosclerosis. This disease, which causes leakage of protein into the urine, is relatively common in these age groups, causes kidney failure in many cases, and has been highly resistant to therapy.

A trial network for polycystic kidney disease has been established with four clinical centers and a data coordinating center. This group is in the final phase of devising a treatment trial for this hereditary kidney disorder.

Item

Mucopolysaccharidosis (MPS) – The Committee is pleased with the efforts made by the NIDDK to enhance research efforts in the area of MPS, both to achieve a greater understanding of these disorders and to pursue the development of effective therapies. The Committee encourages the NIDDK to continue its strong investment in MPS-related research, including bone and joint involvement and pathophysiology of brain damage as they relate to MPS disorders. The NIDDK is further encouraged to build on collaborative efforts with the NINDS, NICHD and appropriate Institutes and Centers involved in this research. **(Page 111)**

Action Taken or to be Taken

As a result of the NIDDK's July 2001 co-sponsorship of a Request For Applications (RFA) with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Child Health and Human Development (NICHD), the National Institute on Aging (NIA), and the National Institute of Deafness and Communication Disorders (NIDCD) on "Gene Therapy for Neurological Disorders," the Institute has funded two MPS-related grants. Knowledge gained from these studies will advance progress toward treatment of the neurological symptoms of MPS and MPS-like lysosomal storage disorders. In September 2002, the NIDDK co-sponsored a workshop with NINDS, NICHD, and the Office of Rare Diseases (ORD), entitled "The Mucopolysaccharidoses: Therapeutic Strategies for the Central Nervous System." The goal of this workshop was to explore methods of delivering treatments for lysosomal storage diseases to the central nervous system, which is the main barrier to treatment. If successful, such therapies may be able to alleviate brain damage caused by these diseases. This year, NIDDK-supported researchers made a significant breakthrough in treatment of mucopolysaccharidosis VII in dogs. In the study, scientists used a retroviral vector to insert a functional copy of the gene for beta-glucuronidase (the critical enzyme lacking in MPS VII) into liver cells of dogs with MPS VII. Their hope was that the liver cells would manufacture the enzyme and release it into the bloodstream to be carried to other affected organs. The treatment worked, preventing heart, eye, bone, and joint abnormalities, and other symptoms that the scientists

could assess. This research may one day lead to human gene therapy treatments not only for MPS VII, but also for other lysosomal-storage or enzyme-deficiency diseases.

Item

Non-alcoholic steatohepatitis – The Committee is pleased that the Institute has provided funding for six clinical centers and one data coordinating center to focus additional research on non-alcoholic steatohepatitis (NASH), which is the second most common cause of liver disease after hepatitis C. In view of the fact that NASH is increasing rapidly in children, the Institute is encouraged to collaborate with the NICHD to expand this award to include a more significant focus on children. **(Page 112)**

Action Taken or to be Taken

In response to a Request for Applications issued in FY 2001, the non-alcoholic steatohepatitis (NASH) Clinical Research Network of eight clinical centers and a data coordinating center were established. This Network will enroll a large number of patients with NASH to accelerate clinical research and progress in understanding the pathogenesis of NASH, defining its natural history, and developing safe and effective means of treatment for persons with the disease.

The Network will establish a clinical database of patients with NASH based on the established criteria and definitions, as well as serum and tissue samples. Both pediatric and adult patients will be included along with controls. The database will be designed to address specific questions and to provide appropriate reagents or patient populations for clinical and laboratory investigations. The investigators within the Network are expected to interact with basic and laboratory research investigators outside of the Network, potentially generating separate grant applications for full-scale clinical trials. The Network is being co-funded by the NIDDK and the National Institute of Child Health and Human Development.

Item

Osteoporosis –The Committee encourages the NIDDK to collaborate with the NIAMS to conduct large-scale trials to determine the most effective and least costly way to combine treatments for osteoporosis, both to prevent bone breakdown and build new bone. The Committee also urges the NIDDK to consider co-funding grants with NCCAM and the Office of Dietary Supplements regarding the nutritional and hormonal influences of calcium on bones, as well as the bioavailability of various calcium supplements. **(Page 112)**

Action Taken or to be Taken

A promising prospective treatment for osteoporosis currently under consideration at the Food and Drug administration (FDA) was discussed at the NIDDK-sponsored meeting in April of 2002, entitled "Asymptomatic Primary Hyperparathyroidism." Cosponsors included the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), and several other research societies. Unlike current drugs used to treat osteoporosis, which

slow or halt bone loss, clinical trials have demonstrated that this treatment, known as PTH (parathyroid hormone), actually stimulates bone formation. This meeting encouraged interactions between basic and clinical researchers and helped to identify areas of promising research opportunity in treatment of bone diseases such as osteoporosis.

In May 2002, the NIDDK cosponsored a Request For Applications (RFA) with the National Cancer Institute (NCI) to encourage grant applications investigating how cancerous cells interact with bone to enable tumors to invade bones. Such investigations are relevant to osteoporosis because factors made in bone cells attacked by tumor cells may cause bone growth or loss. A better understanding of these factors would enable the design of drugs to promote bone growth or prevent bone loss. In October 2002, the NIDDK cosponsored a Program Announcement (PA) with the NIA, the National Cancer Institute (NCI), NIAMS, and the National Institute of Dental and Craniofacial Research (NIDCR) to encourage research applications that focus on hormones, growth factors, and cytokines that have the potential to add or remove bone. The long-term objective of this PA is to identify potential targets for drug therapy of bone diseases, including osteoporosis. As with the studies funded through the RFA, knowledge from these studies could lead to development of better drugs to promote bone growth or prevent bone loss.

NIDDK's grants portfolio supports several projects examining the influence of diet, hormones, and disease on the calcium in bones. Topics of investigation include how the nervous system influences individuals' calcium intake, the impact of dietary protein intake on calcium turnover in bones, how hormones control calcium metabolism, bioavailability of calcium in a carbonated dairy calcium soft drink as compared to its availability in milk and calcium-supplemented orange juice, vitamin D and calcium metabolism, celiac disease in osteoporosis, and the impact of dietary magnesium deficiency on bone mineral content. The NIDDK remains committed to the support of research of the nutritional and hormonal influence of calcium on bones and the bioavailability of calcium through various dietary supplements. The Institute will also consider co-funding grants supporting these topics with the National Center for Complementary and Alternative Medicine and the Office of Dietary Supplements.

The NIDDK also actively participates in the Federal Working Group on Bone Diseases, which serves to keep all Federal agencies aware of possibilities for collaboration in bone disease efforts. Working group members participated in the Surgeon General's Planning Workshop on Osteoporosis and Bone Health held in December 2002. The NIDDK will continue to pursue joint projects in osteoporosis with other Institutes and Centers of the NIH and throughout the Federal Government though this working group.

Item

Pediatric kidney disease **–** Although significant strides have been made in understanding kidney disease in adults, much less is known about its complications in children, including obstacles to full growth potential and neurocognitive development. For this reason, the Committee is disappointed that children were not included in a prospective cohort study of chronic renal insufficiency, particularly in light of recent initiatives calling for greater participation of children in studies of this nature. Given the long-term implications when children reach adulthood, the Committee strongly

urges the NIDDK to undertake research into the history and treatment of (1) cardiovascular problems in children suffering from chronic kidney disease, giving careful consideration to the role of hypertension, lipid abnormalities, obesity, cardiovascular calcification and cardiac arrhythmia, and (2) neurocognitive and developmental deficits including learning disabilities, with related issues of chronic neurological, intellectual and emotional impairment; poor linear growth; and abnormal bone formation. **(Page 112)**

Action Taken or to be Taken

The NIDDK established the Chronic Renal Insufficiency Cohort (CRIC) study in late 2001 to enhance understanding of the factors that contribute to the decline in kidney function and the development of cardiovascular disease in patients with chronic kidney disease. CRIC is a seven-year, prospective, multi-ethnic, multi-racial study of approximately 3,000 patients. The data and patient specimens from this study will serve as a national resource for investigating chronic renal disease and cardiovascular disease. The decision to exclude children from this study was made on the advice of experts in clinical trial design and based on concerns raised by the applicants. The study plans to include use of radioactive markers to evaluate renal function. In addition, assessment of cardiovascular disease in children requires different outcome measures than for adults. Finally, a number of aspects of kidney disease require different assessment tools in children than in adults, particularly the pressing need to understand the impact of disease on development.

Because some aspects of chronic kidney disease in children differ substantially from those in adults, the NIDDK is planning a similar investigation in the pediatric population. To help plan for this initiative, the NIDDK convened a meeting in 2002, to hear expert advice on the value of systematically collecting information about children who have or who are at risk for kidney disease. Subsequently, the NIDDK, in collaboration with the National Institute of Neurological Disorders and Stroke, and the National Institute of Child Health and Human Development, issued a Request for Applications (RFA) in FY 2003, that will support a prospective epidemiological study focusing on the problems of children with chronic kidney disease. The primary goals of this study are to determine the risk factors for decline in renal function; the incidence of, and risk factors for, impaired neurocognitive development and function; the prevalence of risk factors for cardiovascular disease; and the long-term effects of growth failure and its treatment. The information obtained from this study will establish natural history and outcome measures for intervention and prevention clinical trials.

Item

Pediatric liver disease – The Committee is pleased that the NIDDK has taken steps to increase research on biliary atresia, the most common cause of liver transplantation in children. The Committee notes that metabolic causes of liver disease and non-alcoholic steatohepatitis (NASH) are also significant causes of liver disease in children. Therefore, it urges additional research focused on these diseases and other forms of pediatric liver disease.

Action Taken or to be Taken

Following issue of a Request for Applications, the NIDDK has recently established a non-alcoholic steatohepatitis (NASH) Clinical Research Network to accelerate research on the causes, contributing factors, complications, and therapy of NASH. The Institute recognizes the importance of studying this disease in children, and thus, the new NASH Clinical Research Network includes a pediatric research component. The Network is being co-funded by the NIDDK and the National Institute of Child Health and Human Development.

Item

[ADPKD] **–** The Committee is pleased to note that both the ARPKD gene discovery (for infantile PKD) and the Intracellular Calcium Channel breakthrough for ADPKD in February 2002 were discovered by NIH-funded scientists. The Committee strongly urges NIDDK to take advantage of this unprecedented PKD research momentum and accelerate its research efforts toward creating effective clinical interventions for the 600,000 Americans afflicted with PKD. **(Page 112-113)**

Action Taken or to be Taken

To provide a forum for discussion of recent important findings in polycystic kidney disease (PKD) research, and to plan for future efforts, the NIDDK sponsored a Strategic Planning Meeting for PKD in July 2002. The meeting was attended by members of the PKD research community, as well as researchers from the broader scientific community, who outlined high priorities for areas of research in PKD. The meeting summary has been placed on the NIDDK web site (http://www.niddk.nih.gov/fund/other/PKDMtg-summary.pdf) to advise members of the research community of the areas of investigation that show promise for future study. The recommendations of the Strategic Planning Meeting were grouped into three objectives. These objectives included defining the pathways that cause, affect, or accelerate PKD; outlining directions for genetic research in PKD; and developing treatments that improve the quality of life and longevity of patients with PKD. For the coming fiscal year, the NIDDK is planning to incorporate all three elements of these recommendations into a Program Announcement that will solicit new grants for advancing PKD research.

Item

Training grants **–** The Committee is very concerned that so few investigators have focused their careers on diseases of the pancreas and pancreatic cancer. The Committee urges the NIDDK to increase the number of training grants, fellowship and career development programs, and seed grants that are specifically aimed at increasing the number of researchers, including young investigators, to pancreatic diseases. **(Page 113)**

Action Taken or to be Taken

Although the NIDDK supports vigorous research training and career development programs and participates in the NIH Loan Repayment Program (which seeks to recruit and retain highly qualified health professionals in clinical and pediatric research through educational loan repayment), the Institute recognizes that the area of research on pancreatic diseases and pancreatic cancer could benefit from more research in this field. The Institute supports fellowships and training in research

relevant to pancreatitis, pancreatic development, and pancreatic cancer, and seeks to augment its research training and other support in diseases and cancer of the pancreas. As one avenue for increasing the number of researchers, including young investigators, in this area, the NIDDK sent representatives to a November 2002 meeting of the American Pancreatic Association to advertise research training and other research support opportunities. The issue of the importance of increased training in this area has also been discussed with the research community in a Digestive Diseases Interagency Coordinating Committee meeting.

Item

Urinary incontinence – Urinary incontinence afflicts approximately 13 million adults in the United States, 85 percent of whom are women. The Committee urges the NIDDK to enhance its support of urinary incontinence research following the recommendations of the Bladder Research Progress Review Group. In addition, the Committee encourages the NIDDK to increase the number of clinical sites in the Urinary Incontinence Treatment Network Initiative. **(Page 113)**

Action Taken or to be Taken

In July 2001, the NIDDK convened the Bladder Research Progress Review Group (Bladder Research PRG) to evaluate the bladder research portfolios of NIDDK and NIH, identify research opportunities, and define unmet needs in bladder research. This group consisted primarily of external scientific advisors with expertise in a broad range of research fields relevant to the basic biology and disorders of the bladder, including neurology and developmental biology. The Bladder Research PRG released its final report in August 2002, and this report is serving as a crucial blueprint for NIDDK planning for bladder research initiatives. The NIDDK will be guided by the recommendations of the Bladder Research PRG in planning future initiatives on urinary incontinence.

In FY 2000, the NIDDK, in collaboration with the National Institute of Child Health and Human Development (NICHD), established the Urinary Incontinence Treatment Network (UITN) to ascertain the long-term effectiveness of the common surgical approaches for the treatment of urinary incontinence in women. In FY 2001, the NIDDK increased the number of clinical centers in the UITN to enhance the ethnic and racial diversity of trial participants. Currently, the NIDDK, with co-sponsorship from the NICHD, supports eight clinical Continence Treatment Centers and a data coordinating center; the NIH Office of Research on Women's Health (ORWH) has also provided support for the establishment of clinical centers. The UITN has developed a protocol to conduct a prospective cohort study comparing two surgical treatments for stress and mixed incontinence, and is currently recruiting patients. In FY 2003, the NIDDK intends to provide additional funds to expand the scope of the UITN.

In addition to planned expansion of the UITN, the Institute has co-funded a Specialized Center of Research with the NIH Office of Research on Women's Health (ORWH) for work on urinary incontinence in women. The focus of this center, one of three that the NIDDK is co-funding with ORWH, is to expand basic knowledge about female urethral, bladder, and pelvic floor function, improve understanding of the natural history of incontinence, and provide information for the development of novel treatments for female urinary incontinence. Both basic and clinical research

projects will be pursued at this center, including one project addressing the impact of diabetes on urinary incontinence. Such studies are highly responsive to the recommendations made by the external scientific members of the Bladder Research PRG for research in this area.

Item

Urological diseases – Urological diseases have a significant impact on men, women and children in this country and represent a major public health issue that will increase as the population ages. The Committee has previously expressed its concern over the adequacy of the urology basic science research effort. The Committee therefore strongly encourages the NIDDK to make the investments in urology research needed to achieve significant improvement in the ability of physicians to diagnose and treat these diseases and to relieve the human suffering they cause. **(Page 113)**

Action Taken or to be Taken

In July 2001, the NIDDK convened the Bladder Research Progress Review Group (Bladder Research PRG) to evaluate the bladder research portfolios of NIDDK and NIH, identify research opportunities, and define unmet needs in both basic and clinical bladder research. This group was comprised mainly of external scientific advisors with expertise in a broad range of research fields relevant to the basic biology and disorders of the bladder, including neurology and developmental biology. The Bladder Research PRG released its final report in August 2002, and this report is serving as a crucial blueprint for NIDDK planning for bladder research initiatives. Already, based upon recommendations contained within this report, the NIDDK has drafted two new solicitations for bladder research for release later in FY 2003. The NIDDK expects to issue a Request for Applications (RFA) on "Basic Research Related to Interstitial Cystitis (IC)," and a Program Announcement (PA) to solicit proposals for "Basic Research Studies on the Biology of the Bladder." Both initiatives intend to expand basic knowledge of the bladder, and of bladder diseases, through support of both pilot studies and more fully developed research project grants.

Basic science research on another set of urological diseases, prostatic diseases, has rapidly progressed over the past several years. However, progress and approaches have been constrained by the limited number of investigators in this field. The complexities of prostate research impede entry of new investigators from outside the field. To foster basic research on prostatic diseases, the NIDDK plans to issue a PA in FY 2003 for Prostate Research Novel Exploratory Teams (Prostate Research NET). Through this PA, the NIDDK will solicit planning grant applications and require the teaming of an established prostate researcher with a researcher from another field, or a new investigator. These teams could then develop novel combined approaches to a problem in prostate research. Ultimately, the goals for the Prostate Research NET are to expand the number of investigators in the field and to introduce novel research technologies and approaches to the field.

In addition to these planned initiatives and expansions, the NIDDK, in collaboration with the National Cancer Institute, and the National Institute for Child Health and Human Development, has already issued a PA, entitled "Development of Cell-Selective Tools for Studies of the Bladder, Prostate, and Genitourinary Tract." The purpose of this PA is to promote the development of research tools and innovative methods that may be applied to studies of individual cell types of the bladder, prostate, and genitourinary tract. Elucidating the function of physiologically relevant,

specialized cell types will enhance researchers' understanding of the function of these organs under healthy and pathological states. This may, in turn, aid in the future development of therapeutics for diseases such as interstitial cystitis, infertility, benign prostatic hyperplasia, prostate cancer, and other malignant and non-malignant disorders of the genitourinary tract, as well as in the discovery and development of novel targets for male contraception. Achieving the goals outlined in this PA is deemed a high priority by both the Bladder Research PRG and the Prostate Research PRG.

Item

Urologist shortage – The Committee is aware of the shortage of urologists entering research careers. It encourages the NIDDK to initiate career development awards appropriate for urologists and other surgeons, taking into account the specific requirements for training and experience that urology residency and fellowship training programs must meet. The NIDDK should consider modifying the current research time requirements and develop alternative career pathways suitable for urologic fellowship training programs. **(Page 113)**

Action Taken or to be Taken

The NIDDK recognizes the urgent need to increase the number of urologists entering research careers and the importance of providing an appropriate award mechanism to foster this process. The NIDDK brought this specific topic to the attention of its National Advisory Council at its September 2002 meeting, as it discussed the broad spectrum of training and career award mechanisms currently available to NIDDK-supported extramural researchers. The Urology Subcommittee of the statutory Kidney, Urology and Hematology Interagency Coordinating Committee also discussed this topic at its last meeting in 2002. Based upon the recommendations of these two advisory groups and in consultation with the National Cancer Institute (NCI), the NIDDK is currently developing a special research career award track that recognizes the special needs and requirements of trainees in urology residency and fellowship programs. The NIDDK, possibly in collaboration with NCI, intends to announce the availability of these special awards through a Program Announcement later in FY 2003.

Item

Urology Interagency Coordinating Committee – Several Federal agencies, including the Department of Defense and the Veterans Administration, have a role in urology research. In order to strengthen trans-institutional research, the Committee encourages the NIDDK to provide funds to the Urology Interagency Coordinating Committee to foster such research. **(Page 113)**

Action Taken or to be Taken

The Urology Subcommittee of the Kidney, Urology and Hematology Interagency Coordinating Committee chaired by the Director, NIDDK Division of Kidney, Urologic, and Hematologic Diseases (KUH), is the key component for coordinating urology research across HHS. To further strengthen and support this committee, the NIDDK recently recruited and appointed a leading

pediatric urologist as the chairperson for this committee. Since this appointment, the Urology ICC has met to discuss the critical shortage of urologists in research, and the committee intends to meet three times in calendar year 2003 to discuss other issues of importance to the urology research community.

Item

Urology research centers – The Committee is impressed with the results produced by the O'Brien urology research centers, which bring together a critical mass of scientists who focus on a particular aspect of urologic disease. The Committee urges the NIDDK to increase the number and funding of these centers and ensure that there is focus on pediatric urology; prostate growth and disease; female urology, including incontinence, infection, interstitial cystitis, and bladder function and development; and tissue engineering and genetics. These centers should also be able to develop exploratory projects and provide support for resident and fellow research opportunities. **(Page 113)**

Action Taken or to be Taken

In Spring 2002, the NIDDK issued a Request for Applications (RFA) for new or re-competing applications for the George O'Brien Urology Research Centers Program, co-sponsored by the National Cancer Institute. Funding is being provided for five centers, contingent upon the receipt of scientifically meritorious applications, to be awarded in late FY 2003. In addition to re-competing this very successful urology research centers program, the NIDDK and the Office of Research on Women's Health (ORWH) co-funded three Specialized Centers of Research in FY 2002 that focus on urological disorders that affect primarily women: interstitial cystitis, urinary tract infections, and urinary incontinence. These specialized centers will further foster urological research by supporting both basic and clinical studies of the bladder and urinary tract.

Item

Women's urological health – The Committee is concerned with the lack of progress at NIDDK in developing a women's urological health initiative. The conference held 4 years ago identified important research issues and needs, but there has been little subsequent action. The Committee strongly urges the Institute to implement the conference recommendations in the coming fiscal year and address the management problems that caused this delay in action. **(Page 113-114)**

Action Taken or to be Taken

The NIDDK has taken significant steps to enhance its strong commitment to research on women's urological health. In July 2001, the NIDDK convened the Bladder Research Progress Review Group (Bladder Research PRG) to evaluate the bladder research portfolios of NIDDK and NIH, identify research opportunities, and define unmet needs in bladder research, including needs particular to women's urological health. The Bladder Research PRG released its final report in August 2002. In FY 2003, based upon recommendations emanating from the Bladder Research PRG report, the NIDDK intends to release two new solicitations for bladder research. The NIDDK will issue a Request for Applications (RFA) on "Basic Research Related to Interstitial Cystitis (IC)," and a Program Announcement (PA) to solicit proposals for "Basic Research Studies on the Biology of the

Bladder." In addition to these planned initiatives, the NIDDK expects to maintain and expand upon its clinical efforts to combat IC through its recently issued RFA, "Interstitial Cystitis Clinical Research Network." This RFA is a recompetition and expansion of the IC Clinical Trials Group established by the NIDDK through an RFA issued in 1997. The ICCTG is engaged in two important trials, one assessing a new therapy for IC symptoms, the other testing combinations of orally administered drugs to combat pain, in addition to studying potential biomarkers for the disease in urine. The NIDDK hopes to fund a second five-year clinical trials group, with enhanced opportunities to develop ancillary studies in conjunction with the clinical trials – a specific goal outlined within the RFA.

In FY 2000, the NIDDK established the Urinary Incontinence Treatment Network (UITN) to ascertain the long-term effectiveness of the common surgical approaches for the treatment of urinary incontinence in women. Currently, the NIDDK, with co-sponsorship from the National Institute of Child Health and Human Development (NICHD), supports eight clinical Continence Treatment Centers and a data coordinating center. The NIH Office of Research on Women's Health (ORWH) has also provided support for the establishment of these clinical centers. The UITN has developed a protocol to conduct a prospective cohort study comparing two surgical treatments for stress and mixed incontinence, and is currently recruiting patients. In FY 2003, the NIDDK intends to provide additional funds to expand the scope of the UITN.

In addition to developing these new and recompeting initiatives, the NIDDK recently co-funded three research grant applications focused on bladder disorders with the NIH ORWH. These three applications, received in response to the ORWH "Specialized Centers of Research" solicitation in FY 2002, are focused on urinary tract infections, urinary incontinence, and IC – all conditions recognized as needing further research support by the Bladder Research PRG, and all conditions that disproportionately affect women. Through both these very important collaborative efforts and its own initiatives, the NIDDK will continue its vigorous response and action for women's urologic health.

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2003 Amount Authorized	2003 Amended President's Budget	2004 Amount Authorized	2004 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,652,420,000	Indefinite	$1,768,180,000
National Institute of Diabetes and Digestive and Kidney Diseases	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/, b/	50,741,000	c/	51,827,000
Total, Budget Authority				1,703,161,000		1,820,007,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Type One Diabetes Authorized by P.L. 105-33, P.L. 106-554 and P.L. 107-360.
c/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1995 2/	$731,500,000	$726,784,000	$728,784,000	$727,628,000 3/
Rescission				(679,000)
1996	748,798,000 2/	771,252,000	738,456,000 2/	771,252,000 4/
Rescission				(670,000)
1997	758,847,000 2/	806,542,000	787,473,000 2/	815,607,000
1998	821,164,000 2/	874,337,000	883,321,000	900,860,000 10/
1999	924,702,000 2/,6/	951,203,000	994,218,000	1,021,218,000 5/,10/
Rescission				(659,000)
2000	1,002,747,000 2/	1,087,455,000	1,130,056,000	1,174,588,000 7/,10/
Rescission				(6,112,000)
2001	1,186,266,000 2/	1,315,530,000	1,318,106,000	1,470,385,000 8/,10/
Rescission				(429,000)
2002	1,457,915,000	1,446,705,000	1,501,476,000	1,563,833,000 9/,10/
Rescission				(453,000)
2003	1,704,226,000 10/			
2004	1,820,007,000 10/			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reductions of $679,000.
4/ Excludes enacted administrative reductions of $670,000.
5/ Excludes enacted administrative reductions of $659,000.
6/ Reflects a decrease of $2,790,000 for the budget amendment for bioterrorism.
7/ Excludes enacted administrative reductions of $6,112,000.
8/ Excludes enacted administrative reductions of $429,000.
9/ Excludes enacted administrative reductions of $453,000.
10/ Includes Type One Diabetes funds.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
Office of the Director	73	85	85
Division of Diabetes, Endocrinology and Metabolic Diseases	25	26	26
Division of Digestive Diseases and Nutrition	19	20	20
Division of Kidney, Urologic and Hematologic Diseases	20	21	21
Division of Nutrition Research Coordination	7	8	8
Division of Extramural Activities	60	61	61
Division of Intramural Research	457	444	433
Total	661	665	654

Statutorily-ceiling exempt FTEs not included above.

Funds to support these FTEs are provided by Cooperative Research and Development Agreements.

FISCAL YEAR	Average GM/GS Grade
2000	11.0
2001	11.0
2002	12.8
2003	12.8
2004	12.9

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Positions

GRADE	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
ES-6	0	0	0
ES-5	0	0	0
ES-4	3	3	3
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	3	3	3
Total - ES Salary	414600	414600	426210
GM/GS-15	45	44	43
GM/GS-14	59	58	57
GM/GS-13	49	52	51
GS-12	55	55	54
GS-11	48	48	46
GS-10	3	3	5
GS-9	54	56	53
GS-8	31	31	32
GS-7	42	45	42
GS-6	10	8	8
GS-5	7	9	8
GS-4	7	5	4
GS-3	0	0	0
GS-2	0	0	0
GS-1	0	0	0
Subtotal	410	414	403
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	8	9	9
Senior Grade	6	7	7
Full Grade	1	1	1
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	15	17	17
Ungraded	251	254	259
Total permanent positions	401	397	386
Total positions, end of year	687	690	695
Total full-time equivalent (FTE) employment,end of year	661	665	654
Average ES level	ES-4	ES-4	ES-4
Average ES salary	138200	138200	142070
Average GM/GS grade	12.8	12.8	12.9
Average GM/GS salary	88773	88773	91259